Individual participant data meta-analysis of 14 randomized trials evaluating prophylactic heparin in ambulatory cancer patients

Authors:

Prof Holger J Schünemann, MD, Matthew Ventresca, MSc, Prof Mark Crowther, MD, Matthias Briel, MD, Qi Zhou, PhD, Prof Simon Noble, MD, Prof Fergus Macbeth, MD, Prof Gareth Griffiths, MD, Prof David Garcia, MD, Prof Gary H Lyman, MD, Marcello DiNisio, MD, Prof Alfonso Iorio, MD, Lawrence Mbuagbaw, MD, Ignacio Neumann, MD, Nick Van Es, MD, Prof Gordon Guyatt, MD, Prof Michael B Streiff, MD, Maura Marcucci, MD, Tejan Baldeh, MPH, Prof Ivan D Florez, MD, Ozlem Gurunlu Alma, PhD, Ziad Solh, MD, Prof Patrick M Bossuyt, PhD, Lara A Kahale, PhD, Prof Walter Ageno, MD, George Bozas, MD, Prof Harry R Büller, MD, Prof Bernard Lebeau, MD, Ramon Lecumberri, MD, Prof Charles Loprinzi, MD, Prof Robert McBane, MD, Kostandinos Sideras, MD, Prof Anthony Maraveyas, MD, Uwe Pelzer, MD, Prof James Perry, MD, Clara Klerk, MD, Prof Giancarlo Agnelli, MD, Prof Elie A Akl, MD, and the IPDMA heparin use in cancer patients research group

1. Michael G. DeGroote Cochrane Canada and McGRADE Centres, Department of Health Research Methods, Evidence and Impact, Faculty of Health Sciences, McMaster University, Hamilton, Canada (Prof H J Schünemann MD, M Ventresca MSc, M Briel MD, Q Zhou PhD, Prof A Iorio MD, L Mbuagbaw, MD, I Neumann MD, N Van Es MD, Prof G Guyatt MD, M Marcucci MD, T Baldeh MPH, Prof I D Florez MD)
2. Department of Medicine, McMaster University, Hamilton, Ontario, Canada (Prof H J Schünemann MD, Prof Mark Crowther MD)
3. Department of Clinical Research, Basel Institute for Clinical Epidemiology and Biostatistics, University of Basel and University Hospital Basel, Basel, Switzerland (M Briel MD)
4. Marie Curie Palliative Care Research Centre, Cardiff University, Wales, UK (Prof S Noble MD)
5. Centre for Trials Research, College of Biomedical & Life Sciences, Cardiff University, Wales, UK (Prof F Macbeth MD, Prof G Griffiths MD)
6. Faculty of Medicine, University of Southampton, Southampton General Hospital, Southampton, UK (Prof G Griffiths MD)
7. University of Washington School of Medicine, Seattle, Washington, USA
8. Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA (Prof D Garcia MD, Prof G H Lyman MD)
9. Department of Medicine, University of Washington School of Medicine, Seattle, Washington, USA (Prof G H Lyman D)

10. Department of Medicine and Ageing Sciences, University G. D'Annunzio, Chieti-Pescara, Italy (M DiNisio MD)
11. Department of Vascular Medicine, Amsterdam University Medical Center, location AMC, Amsterdam, The Netherlands (M DiNisio MD, N Van Es MD, Prof H R Büller MD)
12. Division of Hematology, Department of Medicine, Hamilton, Ontario, Canada (Prof A Iorio MD)
13. Biostatistics Unit, Father Sean O'Sullivan Research Centre, St Joseph's Healthcare, Hamilton, Ontario, Canada (L Mbuagbaw MD)
14. Department of Internal Medicine, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile (I Neumann MD)
15. Division of Hematology, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA (Prof M B Streiff MD)
16. Department of Paediatrics, Universidad de Antioquia, Medellin, Colombia (Prof I D Florez MD)
17. Department of Statistics, Mugla S tk Kocman Unv, Mugla, Turkey (O G Alma PhD)
18. Transfusion Medicine Section, Department of Pathology & Laboratory Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada (Z Solh MD)
19. Department of Clinical Epidemiology, Biostatistics, and Bioinformatics, Amsterdam Public Health Research Institute, Amsterdam University Medical Centers, Amsterdam, The Netherlands (Prof P M Bossuyt PhD)
20. Department of Internal Medicine, American University of Beirut, Lebanon (L A Kahale PhD, Prof E A Akl MD)
21. Department of Medicine and Surgery, University of Insubria, Varese, Italy (Prof W Ageno MD)
22. Academic Department of Medical Oncology, Castle Hill Hospital, Cottingham, Hull University Teaching Hospitals NHS Trust,UK (G Bozas MD)
23. Service de Pneumologie, Hôpital Saint-Antoine, Assistance Publique—Hôpitaux de Paris, Université Pierre et Marie Curie, Paris, France (Prof B Lebeau MD)
24. Hematology Service, University Clinic of Navarra, Pamplona, Spain. CIBER-CV. (R Lecumberri MD)
25. Divisions of Cardiology and Medical Oncology, Mayo Clinic, Rochester, Minnesota, USA (Prof C Loprinzi MD)
26. Divisions of Vascular Medicine and Hematology, Mayo Clinic, Rochester, Minnesota, USA (Prof R McBane MD)
27. Divisions of Medical Oncology and Hematology, Mayo Clinic, Rochester, Minnesota, USA.(K Sideras MD)
28. Division of Cancer-Hull York Medical School, University of Hull, Hull, UK (Prof A Maraveyas MD)
29. Division of Hematology, Oncology and Tumor Immunology, Charité - Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt Universität - Universität zu Berlin, Berlin Institute of Health, Berlin, Germany (U Pelzer MD)
30. Division of Neurology, Sunnybrook Health Science Centre, Toronto, Canada (Prof J Perry MD)
31. Ontario Clinical Oncology Group and Department of Oncology, McMaster University, Hamilton, Canada (Prof J Perry MD)
32. Department of Internal Medicine, Dijklanderziekenhuis, Hoorn, The Netherlands (C Klerk MD)

33. Internal and Cardiovascular Medicine-Stroke Unit, University of Perugia, Perugia, Italy (Prof G Agnelli)

Corresponding author:
Prof. Holger Schünemann
Michael G DeGroote Cochrane Canada and McMaster GRADE centres; Department of Health Research Methods, Evidence and Impact, McMaster University, HSC-2C, 1280 Main St West; Hamilton, ON L8N 3Z5, Canada;
Email: schuneh@mcmaster.ca
Phone Number: 1 905 525 9140 x 24931
Fax Number: 1 905 522 9507

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LMWH reduces VTE without increasing bleeding but does not improve survival across all patients.

Summary (Word count: 250/250)

Background: A study-level meta-analysis provides high certainty evidence that heparin reduces the risk of symptomatic venous thromboembolism (VTE). It remains unclear if benefits and harms differ by cancer type. This individual participant data meta-analysis of randomized controlled trials (RCTs) examines the impact of heparin on survival, VTE, and bleeding in cancer patients in general, and by cancer type.

Methods: We systematically searched MEDLINE, EMBASE, and The Cochrane Library for RCTs comparing parenteral anticoagulants to placebo or standard care among ambulatory patients with solid tumors and no indication for anticoagulation until January 2017 and updated it to May 2020 without language restrictions. We calculated the impact on mortality and VTE occurrence through multivariable hierarchical models with patient-level variables as fixed effects and a categorical trial variable as a random effect, adjusting for age, cancer type and metastasis status. Interaction terms were tested to investigate effects in predefined subgroups.

Findings: We obtained data from 14 of 19 RCTs (8,278 of 10,041 participants). Meta-analysis revealed an adjusted relative risk (RR) of mortality at one year of 0.99 (95% CI: 0.93, 1.06) and a hazard ratio of 0.99 (95% CI: 0.94, 1.05). The adjusted RR for VTE was 0.58 (95% CI: 0.47, 0.071), for major bleeding 1.27 (95% CI: 0.92, 1.74), and for minor bleeding 1.34 (95% CI: 1.19, 1.51). Subgroup analysis of VTE occurrence by cancer type identified the most certain benefit from heparin treatment in patients with lung cancer RR=0.59 (95% CI: 0.42, 0.81) which dominated the overall reduction in VTE. Certainty of the evidence for the outcomes ranged from moderate to high.

Interpretation: LMWH reduces risk of VTE without importantly increasing risk of major bleeding but does not prolong survival.

Evidence before this study

We previously conducted a study-level systematic review and meta-analysis suggesting that cancer patients may experience a survival benefit from prophylactic heparin, in addition to the reduction in venous thromboembolism. There also was uncertainty if antithrombotic effect differs by cancer subtype. These analyses were based on a search of MEDLINE, EMBASE, and the Cochrane Library databases for randomized controlled trials comparing parenteral anticoagulants to placebo or standard care among patients with solid cancer until February 2016. Patients had no indications for prophylactic or therapeutic anticoagulation and were ambulatory. Search terms included “heparin”, “cancer”, “clinical trial” as well as the names of various types of low-molecular weight heparin. We placed no language restrictions. Study level meta-analyses limited in-depth exploration of subgroup effects leading our research team to conduct an individual participant data meta-analysis.

Added value of this study

To our knowledge, this is the first individual participant data meta-analysis investigating the effects of heparin use on patient important outcomes for cancer patients. Our analysis indicates that heparin does not prolong survival and it appears to have no direct clinical antitumor effect. However, there are VTE risk reductions for patients with breast, lung, colon/prostate, lung, pancreatic and other types of cancer, without importantly increasing the risk of major bleeding or thrombocytopenia. However, minor bleeding appears to be increased. Where power permitted, subgroup analyses exploring differential effects of LMWH by cancer type did not identify any significant associations for mortality or VTE outcomes. The primary strength of this study is the consolidation of high-quality patient-level data from 14 randomised clinical trials and their combination through rigorous and standardised analysis. This meta-analysis included a heterogeneous population in terms of types of cancer. However, with slightly more than half of the patients having lung cancer only 4 specific types of cancer demonstrated sufficient

representation to support specific analysis. Additional research examining the effects of LMWH by type, dose, and schedule may be required and should include quality of life outcomes.

Implications of all the available evidence

This study supports that LMWH prophylaxis decreases the risk of VTE by almost half without importantly increasing the risk of major bleeding or thrombocytopenia, but that of minor bleeding. Heparin in this setting does not prolong survival. Our findings are relevant for guidelines, in particular those by the American Society of Hematology, which use these data in its upcoming guidelines. Our study level meta-analyses have also been used in guidelines of the American Society of Clinical Oncology and the International Society on Thrombosis and Haemostasis. Depending on the values a patient assigns to the different outcomes, patients may opt for or against prophylaxis. This data also needs to be seen in context of new data emerging about new direct oral anticoagulants. Other basic and clinical research should focus on a comparison with new direct oral anticoagulants that seem to have similar effects on venous thromboembolism but less data on bleeding risk.

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Background (349 words)

Cancer is a leading cause of death worldwide. The International Agency for Research on Cancer estimated that over 14 million new cancer cases were diagnosed in 2012, and this number is expected to grow to over 17 million in 2020.(1) The risk of venous thromboembolic complications is elevated in patients with cancer.(2, 3) The annual risk of suffering a venous thromboembolic event (VTE) in patients with solid cancer is 4–5% overall with wide variation across tumour types.(4) Patients who experience VTE frequently require hospitalisation and/or prolonged anticoagulant therapy. VTE in cancer patients is also associated with functional impairments in day-to-day life, pain and significant increase in costs of care.(5)

Heparins are administered parenterally by intravenous infusion or subcutaneous injections.(6) It has been speculated that heparins may improve outcomes in patients with cancer through an anti-tumour effect, in addition to their antithrombotic effect.(7) This possible anti-tumour activity of heparin, mechanistically, involves the inhibition of cell–cell interaction by blocking cell-adhesion molecules (selectins), the inhibition of extracellular matrix protease heparinase and the inhibition of angiogenesis.(8)

However, anticoagulants may increase the risk for bleeding and this risk is likely higher in patients with cancer. Heparins are also known to cause heparin-induced thrombocytopaenia.(9) These observations led to numerous trials evaluating the role of heparins in cancer survival, while subsequent systematic reviews and guideline panels began to evaluate the benefits and harms of prophylactic heparin use in patients with solid tumors.(10-15) Our previous study level meta-analyses suggested a survival benefit and a large reduction in VTE in favour of heparins.(4, 16) However, study level meta-analyses have limitations which include not allowing in-depth exploration of subgroup effects. Therefore, we conducted an individual patient data

meta-analysis (IPDMA) to examine the following questions: 1) Is survival prolonged by the administration of prophylactic anticoagulation?; and 2) Are there specific subgroups of cancer patients for whom the benefit is more robust?

Methods

We conducted this systematic review according to Cochrane Collaboration standards, registered it in the International Prospective Register for Systematic Reviews (PROSPERO, CRD42013003526)(17) and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data (PRISMA-IPD) guidelines.(18) We previously published the study protocol and, therefore, will describe the methods here only briefly.(19)

Inclusion criteria

Types of Participants: Patients with solid cancers with no other indication for prophylactic anticoagulation (e.g. acute illness, central venous line placement, perioperative status) or therapeutic anticoagulation (e.g. for the treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE)). We included studies in which patients received concomitant chemotherapy or radiotherapy as long as these treatments did not impact on randomization to heparin or no heparin.

Types of intervention: parenteral anticoagulants such as UFH, LMWH, and fondaparinux.

Comparator intervention: placebo or standard care.

Study designs: We considered randomized controlled trials (RCTs) comparing parenteral anticoagulants to placebo or standard care.

Literature search

We conducted a search of the following electronic bibliographic databases (Table S1):(16) MEDLINE, EMBASE, and the Cochrane Library (including Cochrane Central Register of

Controlled Trials/CENTRAL, Clinical Trials, DARE and NHS EED) from inception until January 2017. An updated search was completed in May of 2020, studies published during this period are included in sensitivity analysis which compares study-level meta-analysis to our individual participant data meta-analysis. To identify additional studies, we also used the 'related article' feature in PubMed and reviewed references of identified studies, narrative review articles, and conference proceedings of the American Society of Clinical Oncology as well as the American Society of Hematology. We applied no date or language restrictions to included trials.

Two reviewers independently assessed titles and abstracts of all identified citations for potential eligibility (Figure 1). Two reviewers screened full texts for eligibility using a standardised pilot tested form with explicit inclusion and exclusion criteria. Decisions were compared and agreement was measured using the Kappa (κ) statistic.(20) Disagreements were resolved by consensus and, when needed, with the help of a third reviewer. Reasons for exclusion were recorded.

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. In addition to the study protocol and complete analysis plans, a detailed list of all variables of interest was provided to contacted trialists in order to maintain analytical transparency, to avoid data driven analysis and to encourage authors to share relevant trial data. The study protocol, case report forms and corresponding datasets with all patient identifiers removed were requested. Requested baseline data included participant's anonymized demographic information, cancer diagnosis, concomitant therapies, history of VTE and bleeding, inflammatory markers as well as platelet and haemoglobin measurements. Requested follow-up information included randomisation, treatment start/stop, censoring, and outcome (mortality, VTE, bleeding, thrombocytopenia and health related quality of life) occurrence dates. We required DVT events be diagnosed using an objective diagnostic test such as: venography, or compression ultrasound and included any DVT events recorded in

shared data regardless of their occurrence in lower or upper extremities. Pulmonary embolism events had to be diagnosed using an objective diagnostic test such as: pulmonary perfusion/ventilation scans, computed tomography pulmonary angiography or autopsy. We accepted trial authors' definitions for bleeding (Appendix page 5). We were unable to obtain sufficiently comparable data describing health related quality of life which we had planned in the study protocol.(19) All shared data were stored on secure password-protected servers. To ensure that the data provided correspond to the reported results, we cross-checked baseline data and recalculated primary analyses. We contacted trial authors to resolve discrepancies between shared data and published results.

Assessment of risk of bias and overall certainty of evidence

Two review authors assessed, in duplicate and independently, the risk of bias according to Cochrane methods. Disagreements were resolved by discussion or with the help of a third reviewer. We used the following criteria to assess the risk of bias: allocation concealment; blinding of participants, healthcare providers, data collectors, outcome adjudicators, and data analysts; completeness of available data; and stopping early for benefit. We assessed selective outcomes and other reporting bias by comparing outcomes in published protocols and in the methods section to the outcomes reported in the published paper. We assessed statistical heterogeneity by calculating the Chi^2 and its p-value, and the I^2. We recorded and reported the sponsorship of included trials (whether sponsored by a for-profit or not-for-profit organisation or government agency) and assessed financial and intellectual conflicts of interest. Inverted funnel plots were generated for each comparison to detect possible publication bias.

We used Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profiles to summarise the intervention effects following the GRADE approach (21, 22) to provide support for decision makers. We used GRADE's GRADEpro software.(23) To

perform the GRADE assessment, we assessed publication bias and heterogeneity by using study-level identifiers. We conducted this assessment for the relative estimates of effect as well as baseline risk estimates in various patient subgroups.

Datasets and data extraction

Two review authors independently extracted individual participant data and aggregate level data in duplicate using standardised pre-piloted data extraction forms. We standardised variable names and value labels across trials. Data were initially entered into an Excel database and converted to SAS for analysis. Finally, we synthesized data sets and assigned a coded trial variable for each participant. The percentage of missing data in analyses relevant variables was calculated and Little's method was used to assess the missing completely at random (MCAR) assumption in the variables with at least 5% of missing data. If the MCAR assumption was violated, we further examined the MAR pattern by comparing the outcome in the variable with and without missing values.

Data analysis

All analyses followed the intention-to-treat (ITT) principle. We summarised categorical data using frequencies alongside percentages and continuous data with mean or median, depending on the distribution, together with standard deviation (SD) or interquartile range (IQR). For dichotomous outcomes, we expressed the intervention effects in relative risk (RR).

A one-stage approach was used to analyze data. In the regression analyses, we used multilevel models(24-26) to incorporate data at trial level and patient level. We included four adjustment variables - age, time to cancer diagnosis prior to baseline, cancer type and stage of cancer - as fixed effects and trial as a random effect. Therefore, heterogeneity among trials was modelled with the frailty random effect.

The regression modeling was based on the joint distribution of the treatment effect and trial with a bivariate normal distribution (i.e., using model (3) from Turner et al.(26)). As Poisson regression takes into account that different observations have different lengths of follow-up, we used the mixed robust Poisson regression model to estimate the adjusted RR. We also performed a multilevel Cox regression analysis with frailty random effects for trials and used the hazard ratio (HR) to express the intervention effect for the time to mortality analysis. In order to account for death as a risk competing with the development of VTE, a competing risk model based cumulative incidence curve was plotted for time to VTE (27, 28).

Aiming to reduce bias and increase precision, we applied multiple imputation for all the regression analyses depicted above. We performed each regression analysis five times using five data sets with the missing data imputed based on both baseline and outcome data; we calculated pooled estimates along with the 95% confidences and corresponding P-values for each analysis.(29) We also calculated the anticipated absolute effects based on the adjusted RR, and three assumed baseline risks, in terms of the median or mean difference in survival.

In addition, we performed the following pre-specified sensitivity analyses to investigate differences in summary effect estimates related to the conduct of our methods:

1. We compared the main IPDMA results with the results of study-level meta-analysis using the studies we received the original datasets for.
2. We evaluated if higher risk of bias in the original study compared to lower risk of bias may be associated with a greater effect.

We also explored the heterogeneity in the summary effect estimates related to different patient subgroups. We tested the subgroup effect on an interaction term with the treatment in the mixed-effect Poisson regression model with the five adjustment variables including trial as random effect listed as above. This approach is preferred to separate subgroup group-specific analyses.(30, 31) The subgroup factors considered were:

1. Type of cancer

2. Stage of cancer (local compared to metastatic)
3. Concomitant treatment (chemotherapy compared to no chemotherapy)
4. Eastern Cooperative Oncology Group/World Health Organization (ECOG/WHO) performance status(32)
5. Heparin type
6. We compared heparins registered for use by the FDA and EMA to those not registered (semuloparin, certoparin).

As described in our study protocol(19), we initially planned to examine differences in LMWH dose and schedule but due to the high number of variations between studies, we were unable to perform these subgroup analyses.

We used SAS V.9.4 (Cary, North Carolina, USA) to analyse data. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Study authors with access to shared clinical trial data included HJS, MV, and QZ. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results (word count: 843)

Our search identified 8,388 studies, out of which 19 RCTs (with 10,041 participants) fulfilled eligibility criteria. We were able to obtain individual participant data for 14 RCTs representing 8,278 (82.4%) participants (Figure 1).(33-45) Data from the Fragmin Advanced Malignancy Outcome Study (FAMOUS)(46) trial (n=374; 3.7%) was no longer stored electronically and study authors could not convert to a shareable electronic format. The request for PROphylaxis of ThromboEmbolism during CHemoTherapy (PROTECHT)(47) data (n=1,150; 11.5%) was denied due to ongoing analysis which discouraged sponsors from sharing individual participant data. Data from three trials(48-50) (n=239, 2.4%), could not be obtained in a timely fashion.

Figure 1 and Appendix p 7 describe the analyzed studies, Appendix p 11 describes characteristics of studies we were unable to obtain data for. Our updated search identified one additional eligible study, (RASTEN n=377; 4.5%).(51)

We observed the following differences between clinical trial datasets and published results. In the trials conducted by Weber et al.(45) and Lebeau et al.,(37) the shared individual participant data appeared to have been updated beyond the date of the original publication, and included a larger number of deaths. The paper describing the trial by Lecumberri et al.(38) reported that 7 participants in the control group survived 1 year, whereas the corresponding value in the shared participant data was 10. We could not locate the original analysis code to address the discrepancy. For the TOPIC-1(35), individual patient data indicated that 3 symptomatic PE events occurred whereas the publication indicated that only 2 events occurred. The corresponding author no longer had access to the shared study data. In the data from Altinbas et al.(34) the shared data did not specify which participant experienced the reported DVT and we were unable to clarify this.

Included trials were published between 1994 and 2016 and recruited participants from over 50 countries (Appendix p 5). Pooled baseline characteristics were similar between treatment arms (Table 1). All 8,278 patients were adults with a mean age of 61.3 years (SD=10.4), and 61.1% (5,061) were men. The most common types of cancer among participants were those of the lung (55.6%, n=4,573) followed by colon/prostate (15.2%, n=1,247), pancreatic (10.0%, n=823) and breast (5.1%, n=419). Participants allocated to treatment arms (n=4,139) received semuloparin (38.8%, n=1,608), dalteparin (33.1%, n=1,369), certoparin (10.7%, n=442), nadroparin (9.7%, n=402), enoxaparin (3.9%, n=160), calciparin (3.3%, n=138) or bemiparin (0.48%, n=20) subcutaneously for a range of five weeks to approximately two years. Compliance, measured through daily charting and by examining the number of empty syringes returned at follow-up, exceeded 90% in each study which provided relevant individual participant data (Appendix p 13).(33, 35, 38, 42, 44) Approximately 68% (n=5,517) of participants

with available data (n=8,152), presented with metastatic cancer at baseline and 88% (6,988/7,928) received chemotherapy. Trials generally excluded participants with a Karnofsky performance score below 60, ECOG/WHO performance status equal to or above 3, life expectancy of fewer than 3 months, other indication for thromboprophylaxis and a history of bleeding. The median time of intervention, for participants with available data, is 123 days (IQR: 67 to 179) and the median follow-up duration for all participations is 280 days (IQR: 156 to 383). Appendix p 14 summarizes authors' judgements of each risk of bias item for the included studies.

Overall mortality was 65.0% (2,690/4,139) in the LMWH group and 66.4% (2,749/4139) in the control group. The adjusted relative risk of experiencing mortality was 0.98 (95% CI: 0.93, 1.04) throughout trial duration, 0.99 (95% CI: 0.93, 1.06) within 1 year, and 1.00 (95% CI: 0.95, 1.06) after 2 years (Table 2). The median time to death was 7.83 months (IQR: 4.31 to 12.40) in the LMWH arm and 7.60 months (IQR: 4.01 to 12.30) in the control group. The anticipated absolute difference is 0.6% fewer deaths (95% CI: 4 fewer to 3.5 more) within 1 year among those taking LMWH (Table 3). The hazard ratio for time to death, adjusted for age, cancer type, stage of cancer and study (by random effect), was 1.01 (95% CI: 0.96, 1.07) (Appendix p 15). No significant interaction effects were identified (Appendix p 16 - 18).

Of 7,917 participants with available data, the total number of patients experiencing incidental or symptomatic VTEs was 158 of 3,958 (4.0%) in the LMWH group versus 279 of 3,959 (7.0%) in the control group, adjusted relative risk 0.58 (95% CI: 0.47, 0.71). The anticipated absolute difference for incidental or symptomatic VTEs is 3.0% fewer events (95% CI: 3.7 fewer to 2.0 fewer) among those taking LMWH (Table 3). The unadjusted hazard ratio for time to VTE is (HR=0.60; 95% CI: 0.48, 0.74). Symptomatic VTEs occurred in 114 participants in the LMWH group and 220 in the control group, adjusted relative risk 0.58 (95% CI: 0.48, 0.70) (Table 2, Figure 2). The anticipated absolute difference is 2.5% fewer (95% CI: 3.1 fewer to 1.8 fewer) among those taking LMWH (Table 3). Subgroup analysis did not detect any significant interaction (Appendix pages 20 - 22).

Major bleeding events occurred in 1.7% of control (71/4,139) and 2.1% (88/4,139) of LMWH allocated participants, respectively, with an adjusted relative risk of 1.27 (95% CI: 0.92, 1.74) for a risk difference of 0.4% more in LMWH patients (95% CI: 0.3 fewer to 1.3 more, Table 3). Minor bleeding events occurred in 12.1% (478/4,139) of the control population and 16.6% (652/4,139) of LMWH exposed participants, with adjusted relative risk of 1.34 (95% CI: 1.19,

1.51) and risk difference of 4.1% more (95% CI: 2.3 more to 6.2 more). The total incidence of thrombocytopenia was 8.9% (251/2,823) in the control group and 8.7% (244/2,818) in the LMWH group, respectively, with an adjusted relative risk of 0.95 (95% CI: 0.80, 1.14) (Table 2). We found no significant interaction effects for major bleeding, minor bleeding, or thrombocytopenia (Appendix p 23 - 25).

A study-level meta-analysis, including the same studies we obtained individual participant data for, comparing LMWH to no LMWH for each outcome is available in the supplementary material (Appendix p 26 - 34). A funnel plot for the primary outcome of mortality at 12 months indicates no publication bias is present (Appendix p 35). Results resemble analysis using individual participant data with no differing conclusions. Additional study-level meta-analysis including all studies eligible for inclusion for the primary outcome of mortality at 1 year depicts similar results to our IPDMA (Appendix p 36). We did not identify statistically significant associations in sensitivity analysis comparing blinded to unblinded studies or when comparing the effects of approved versus unapproved medications (Appendix p 16).

Table 3 presents the summary of findings and certainty of the evidence ratings according to GRADE. We rated down the certainty of evidence for mortality at one year, any VTE, symptomatic DVT major bleeding and thrombocytopenia for imprecision because confidence intervals include non-clinically significant values. We also rated down the certainty of evidence for any symptomatic or asymptomatic VTE for indirectness, as asymptomatic VTE is considered a surrogate outcome. Other outcomes had high certainty of evidence associated with them. Table 3 shows the absolute effects that we estimated based on baseline risks for VTE reduction, any VTE (symptomatic or asymptomatic VTE), symptomatic VTE, symptomatic DVT, symptomatic PE, major and minor bleeding, and thrombocytopenia.

Discussion

To our knowledge, we performed the first IPDMA addressing the effects of heparin on patient important outcomes in patients with cancer. Our analysis indicates that heparin does not prolong survival and it appears to have no direct clinical antitumor effect. However, there are VTE risk reductions for patients with breast, lung, colon/prostate, lung, pancreatic and other types of cancer, without importantly increasing the risk of major bleeding or thrombocytopenia. Where power permitted, subgroup analyses exploring differential effects of LMWH by cancer type did not identify any significant associations for mortality or VTE outcomes.

The primary strength of this study is the consolidation of high-quality patient-level data from 14 randomised clinical trials and their combination through rigorous and standardised analysis. This meta-analysis included a heterogeneous population in terms of types of cancer. However, with slightly more than half of the patients having lung cancer only 4 specific types of cancer demonstrated sufficient representation to support specific analysis. Due to the numerous permutations in type, dose and schedule of LMWH treatment, we were unable to complete all pre-planned subgroup analyses. Additionally, the trial data did not include sufficiently comparable data describing health related quality of life.(19) Although we could not obtain data from six trials, these individual patient data (n=2,153 participants) represent only 20.6% of participants in all potentially eligible studies and, thus, their inclusion would have been unlikely to alter the results. In addition, study level results from these studies do not differ from our findings. Our findings are also similar to results of the TILT phase 3 trial that was not included in our analysis.(52) Noteworthy is also that semuloparin and certoparin contributed a large proportion of the individual patient data but both agents are not approved by regulators. While the subgroup effects did not differ importantly for efficacy endpoints for different drugs or from the study level meta-analysis, it causes some concern about applicability of the findings (Appendix p 16).

Our findings indicate that certain high-risk cancer groups may benefit from use of LMWH to prevent VTE but that there is likely no impact on mortality. Studies included participants that were not selected by stratification tools in terms of their VTE risk and VTE rates in the control arms varied widely between studies. Thus, there was considerable variation in the risk of VTE which is important for weighing possible benefits and harms. However, we describe elsewhere that risk prediction using scores like the Khorana score may not be able to stratify patients with lung cancer based on their VTE risk.(53) Among those with other cancer types, however, a high-risk score is associated with a 3-times increased risk of VTE compared with a low-to-intermediate risk score and for those patients it may be useful to use prophylaxis. Our analysis did not detect increased risk of major bleeding with high certainty, however, may not have been powered to do so. Minor bleeding is increased in patients receiving LMWH. This allows for a balance of the absolute benefits and harms, namely a 3 to 4% reduction in VTE (moderate to high certainty) and a 4% increase in minor bleeding (high certainty) and a 0.4% increase in major bleeding (moderate certainty). This is considered in guidelines, in particular those by the American Society of Hematology (54), which use these data in its upcoming guidelines. Our study level meta-analyses have also been used in guidelines of the American Society of Clinical Oncology and the International Society on Thrombosis and Haemostasis.(55, 56)

These guidelines should be referred to for clinical decisions, as they utilize detailed criteria that should be considered in translating the evidence provided here to recommendations. Depending on the values a patient assigns to the different outcomes, patients may opt for or against prophylaxis. This data also needs to be seen in context of new data emerging about new direct oral anticoagulants.

Additional research examining the effects of LMWH by type, dose, and schedule may be required and should include quality of life outcomes. Other basic and clinical research should

focus on a comparison with new direct oral anticoagulants (DOAC). The living systematic review through which we included the eligible studies will allow us to identify when new studies become eligible and may affect the findings of this analysis, for potential update of this IPD and to put them in context with the RCTs that evaluate DOACs and compare our effects with those trials. (57, 58) The Cassini investigators found a HR of 0.66 (95% CI, 0.40 to 1.09; p = 0.10) for the primary efficacy end point, a composite of objectively confirmed proximal deep-vein thrombosis in a lower limb, pulmonary embolism, symptomatic deep-vein thrombosis in an upper limb or distal deep-vein thrombosis in a lower limb, and death from venous thromboembolism with rivaroxaban compared to placebo in ambulatory patients with cancer after 180 days.(57) The AVERT investigators observed a HR for venous thromboembolism of 0.41 (95% CI, 0.26 to 0.65; p < 0.001) with apixaban compared to placebo in active cancer patients after 180 days. These effects are similar to those we observed for LMWH.(58) The CASSINI and AVERT trials had only 21 major bleeding events combined and, thus, do not allow yet to draw conclusions about the bleeding risk with the same precision compared to our data with 159 events. Balancing the advantages and disadvantages of these approaches of anticoagulation will be influenced by considerations about bleeding but many other decision criteria that guideline panels consider.(59)

Our analysis of the use of heparin in patients with cancer did not identify important differences in survival time at 1 year, 2 years or throughout trial duration. This study supports previous findings that LMWH use decreases the risk of VTE by almost half without importantly increasing the risk of bleeding or thrombocytopenia. For some outcomes, imprecision suggests that more data could help better balancing the potential health benefits and harms. Our IPDMA results have been used in the soon to be published American Society of Hematology Clinical practice guidelines on Venous Thromboembolism(54) and they may inform other guideline development groups.

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Authorship contributions

Conception of the study by HJS and EAA. The design of this study was generated primarily by HJS, EAA, MC, MB, QZ, SN, FM, GG, SM, DG, GL, MDN, AI, GG, and LK**.** HJS, MV, SN, FM, GA, GG, GL, WA, GB, HB, BL, RL, CL, RM, KS, AM, UP, JP, and CK worked to facilitate the data sharing process of at least one of the eligible clinical trials. MV, QZ, TB, LM, IDF, ZS, and OGA extracted relevant data from at least one shared clinical trial into a unified database. QZ performed statistical analysis. HJS, MC, MB, QZ, SN, FM, GG, DG, GL, LK, MDN, AI, IN, MBS, EAA, and MV interpreted the data and HJS and MV drafted the manuscript. All authors revised the manuscript for important intellectual content and approved the final version of the manuscript.

Conflicts of interest

SN reports personal fees from Bayer, personal fees from Boehringer Ingelheim, outside the submitted work. MDN reports personal fees from Daiichi Sankyo, personal fees from Bayer, personal fees from Pfizer, personal fees from Leo Pharma, personal fees from Aspen, outside the submitted work. MBS reports personal fees from Bayer, grants from Boehringer-Ingelheim, personal fees from Daiichi-Sankyo, personal fees from Pfizer, grants from Roche, grants and personal fees from Janssen, grants from NovoNordisk, grants from Sanofi, outside the submitted work. AM reports grants and personal fees from Bristol-Myers Squibb, grants and personal fees from Bayer, personal fees from Daichii Sankyo, outside the submitted work. WA reports personal fees from Sanofi, personal fees from Aspen, grants and personal fees from Bayer, personal fees from Daiichi Sankyo, personal fees from Boehringer Ingelheim, personal fees from Portola, outside the submitted work. Dr. Crowther reports grants and other from Bayer, personal fees from Shionogi, personal fees from Alexion, grants from Leo pharma, personal fees from Pfizer, other from Daiichi, grants from Heart and Stroke Foundation, other from Alnylam, personal fees from Octapharma, personal fees from Bristol-Myers Squibb Canada, personal fees from CSL Behring, personal fees from Alexion, personal fees from Servier Canada, personal fees from Diagnostica Stago, personal fees from Asahi Kasei, outside the submitted work. CL reports personal fees from PledPharma, personal fees from Disarm Therapeutics, personal fees from Asahi Kasei, personal fees from Metys pharmaceuticals, personal fees from OnQuality, outside the submitted work. NvEreports personal fees from Daiichi Sankyo, Personal fees from Leo Pharma, personal fees from Bayer, outside the submitted work.. EAA reports having published a systematic review on the same topic. None of the other authors report any conflicts of interest.

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Figure 1 – PRISMA-IPD study selection flow diagram

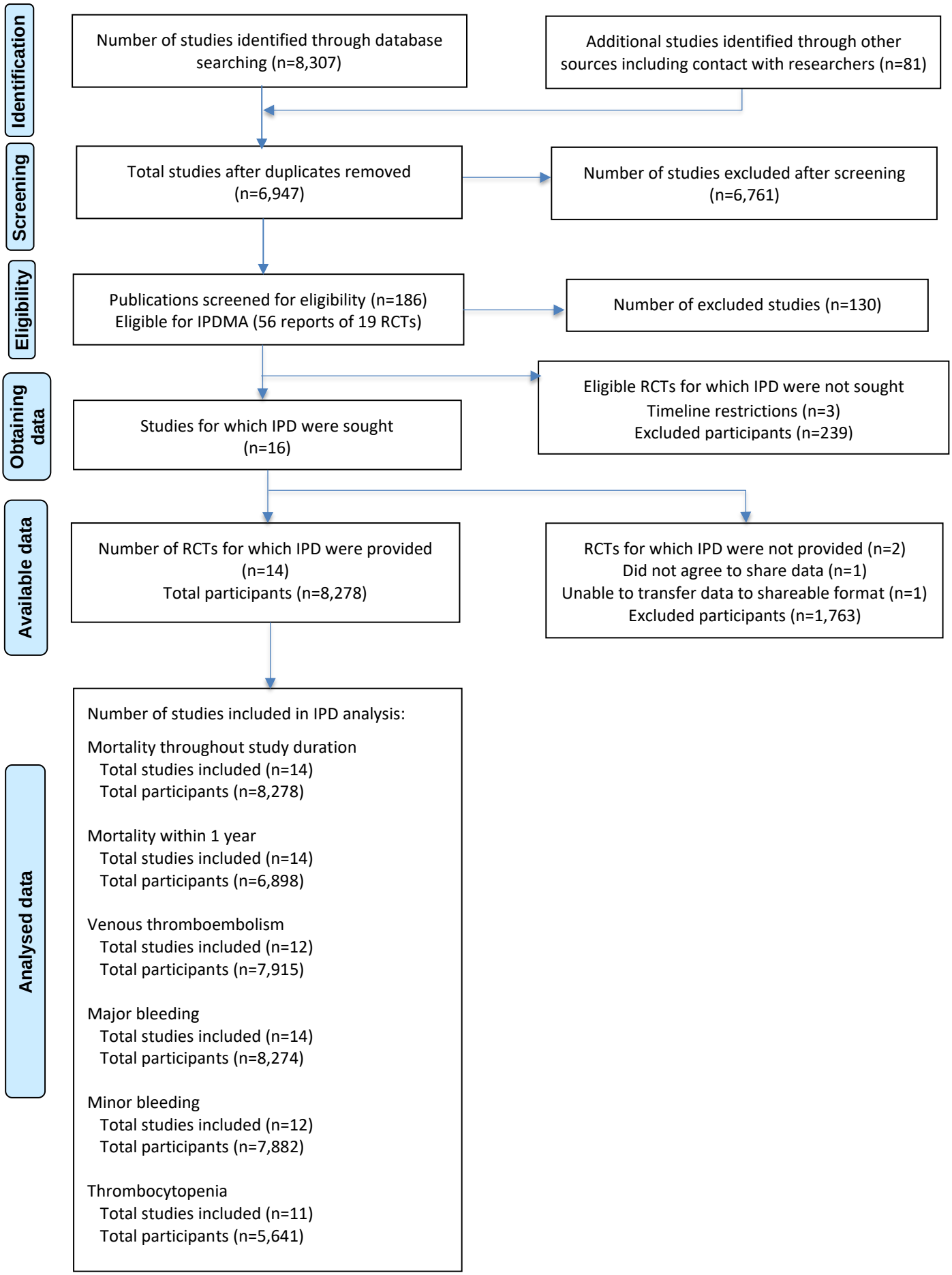
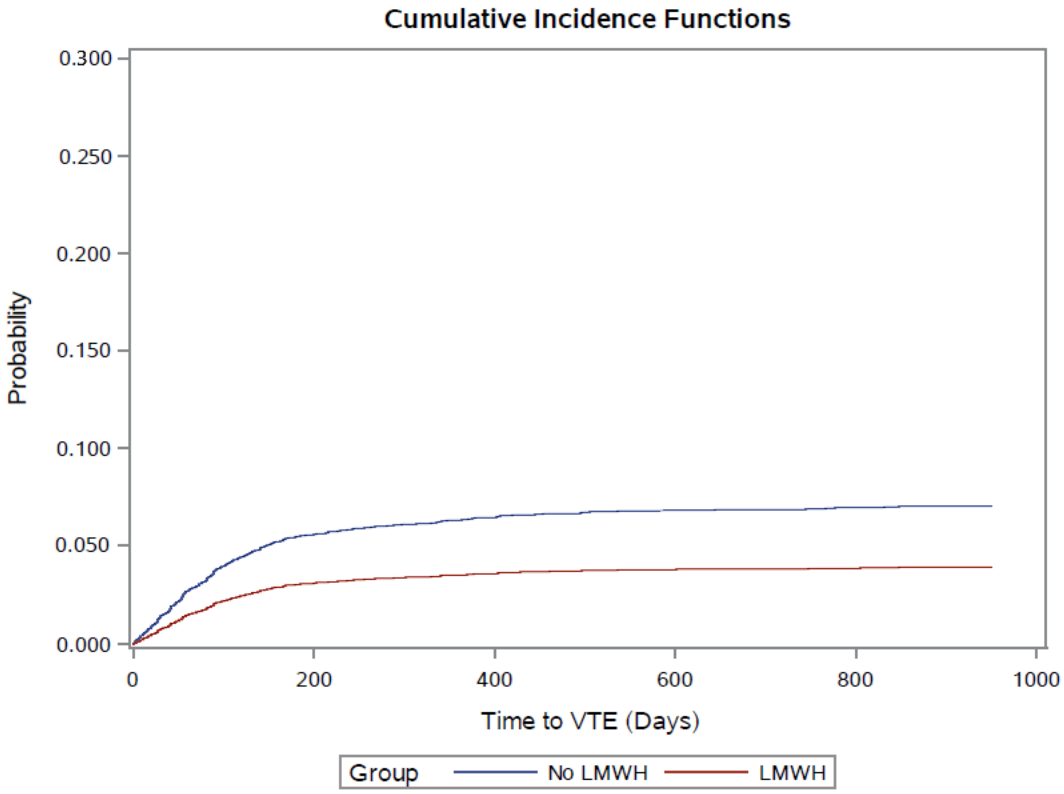


Figure 2. Time-to-event, any asymptomatic or symptomatic venous thromboembolism



Legend. Cumulative Incidence functions for venous thromboembolism in cancer patients on LMWH and no LMWH. Please note that the axis represents a risk from 0 to 30%.