Efficacy and safety of thromboprophylaxis in cancer patients: a systematic review and meta-analysis

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Abstract

Background: Thrombosis is a common complication in patients with cancer. Whether thromboprophylaxis could benefit patients with cancer is unclear. The aim of this systematic review was to determine the efficacy and safety of thromboprophylaxis in patients with cancer undergoing surgery or chemotherapy.

Methods: We searched the Cochrane Library, EMBASE, MEDLINE, EBSCOhost, and Web of Science for studies published before May 2018 to investigate whether thromboprophylaxis measures were more effective than a placebo in patients with cancer.

Results: In total, 33 trials with 11,942 patients with cancer were identified. In patients with cancer undergoing surgery, the administration of thromboprophylaxis was associated with decreasing trends in venous thromboembolism (VTE) [relative risk (RR) 0.51, 95% confidence interval (CI) 0.32–0.81] and DVT (RR 0.53, 95% CI 0.33–0.87). In patients with cancer undergoing chemotherapy, the administration of thromboprophylaxis reduced the incidences of VTE, DVT, and pulmonary embolism compared with no thromboprophylaxis (RR 0.54, 95% CI 0.40–0.73; RR 0.47, 95% CI 0.31–0.73; RR 0.51, 95% CI 0.32–0.81, respectively). The pooled results regarding major bleeding showed no significant difference between prophylaxis and no prophylaxis in either the surgical or the chemotherapy groups (RR 2.35, 95% CI 0.74–7.52, $p = 0.1482$, $I^2 = 0\%$; RR 1.30, 95% CI 0.93–1.83, $p = 0.1274$, $I^2 = 0\%$, respectively).

Conclusion: Thromboprophylaxis did not increase major bleeding events or the incidence of thrombocytopenia. All-cause mortality was not significantly different between those who received thromboprophylaxis and those who did not. This meta-analysis provides evidence that thromboprophylaxis can reduce the number of VTE and DVT events, with no apparent increase in the incidence of major bleeding in patients with cancer.

Keywords: cancer, major bleeding, thromboprophylaxis, venous thromboembolism

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Introduction

Venous thromboembolism (VTE) is a major complication of cancer that occurs in 4–20% of patients with cancer.[1] The incidence of VTE in patients with cancer is 4–7-times higher than in patients without cancer.[2,3] VTE not only prolongs the hospitalization time of patients but is also related to higher medical expenses.[4,5] Furthermore, it complicates the clinical management of cancer and may terminate or delay the required anticancer treatment.[6] The survival rate in patients with cancer with VTE is only one-third of that in other patients with cancer.[7]

Thromboprophylaxis may be beneficial for patients with cancer; however, it also increases the risk of bleeding and thrombocytopenia.[8] Currently, scholars are debating the use of thromboprophylaxis in patients with cancer. Different guidelines give different recommendations

regarding whether to use thromboprophylaxis in patients with cancer. The European Society for Medical Oncology guideline recommends the use of low-molecular-weight heparin (LMWH), unfractionated heparin or fondaparinux in patients with cancer admitted for medical complications, citing lower VTE incidence without increased major bleeding with these drugs compared with the alternatives.[9] The 2017 Asian venous thromboembolism guidelines indicate that in patients undergoing chemotherapy, adequate hydration and frequent mobilization decrease the risk of VTE. Pharmacological prophylaxis may not be indicated.[10] Whether thromboprophylaxis is beneficial for patients with cancer is unclear.

The mechanism underlying VTE in patients with cancer receiving different therapies is multifactorial and includes tissue factor-induced activation of coagulation, stasis as a result of surgery, limb paresis and vessel wall injury due to chemotherapy.[11] In this study, we compared the efficacy and safety of primary thromboprophylaxis to a placebo or no thromboprophylaxis in patients with cancer undergoing surgery or chemotherapy.

Materials and methods

Search strategy and selection criteria

We performed this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[12] (Table S1). The review protocol is available on PROSPERO under registration number CRD42018104521 (www.crd.york.ac.uk/PROSPERO).

We searched the Cochrane Library, EMBASE, MEDLINE, CINAHL and Web of Science databases from 1 January 1960 to 30 May 2018, using a combination of medical subject headings and keywords (Table S2). Reference lists from published meta-analyses and review articles were manually searched to identify any other relevant studies.

Study selection

The titles and abstracts of the identified articles were independently reviewed by two groups of authors to determine their eligibility.

Summary of inclusion and exclusion criteria

Inclusion criteria

- All randomized and quasirandomized trials were eligible.
- Age of patients in the study was >18 years.
- Patients with cancer undergoing surgery or chemotherapy.
- Interventions included parenteral or oral anticoagulants (bemiparin/enoxaparin/dalteparin/warfarin/low-molecular-weight heparin/gemcitabine/apixaban/certoparin/subcutaneous/semuloparin/unfractionated heparin/nadroparin/calcium heparin/LMWH anti-FXa) or mechanical intervention (pneumatic compression).
- The intervention and control arms included placebo, no treatment, standard care, observation, and chemotherapy groups.
- Types of outcome measures: the inclusion criteria included one or more of the following outcomes: venous thromboembolism (VTE)/deep vein thrombosis (DVT)/pulmonary embolism (PE)/major bleeding/all-cause mortality/thrombocytopenia.

Exclusion criteria

- Editorials, reviews, abstracts or conference proceedings.
- Ineligible study designs.
- Controlled studies, observational cohort studies, or case–control studies.
- No relevant population or study setting.
- Patients aged <18 years.
- No relevant intervention or outcome.
- Animal studies.

Data extraction and quality assessment

We extracted the following basic study information from each eligible article: the name of the first author, publication year, country of the study, study design, sample size, demographic and procedural characteristics, diagnostic methods, follow-up duration, details of the experimental interventions, and the clinical and safety outcomes for the patients with cancer. When publications with overlapping populations were available, the publication with the most complete and relevant set of data was chosen.

The primary outcomes of this study were VTE, DVT, and PE in patients with cancer. The secondary outcomes of this study were major bleeding, all-cause mortality and thrombocytopenia.

VTE included asymptomatic or symptomatic PE and DVT. DVT and PE in the same patient was recorded as a single event. VTE, DVT, and PE were diagnosed by Doppler imaging, ventilation/perfusion scanning, computed tomography angiography, venography, or autopsy. Major bleeding was defined as clinically overt bleeding associated with a decrease in the hemoglobin level of at least 2 g/dl or the need for a transfusion of two or more units of packed red cells. Thrombocytopenia was defined as a fall in platelet count below 100,000/ml or a fall >50% from baseline.

Risk of bias was assessed using the Cochrane risk of bias tool,[13,14] and the graphs were generated by Review Manager. The data were separately extracted by two groups of authors, and data comparison, quality assessment and verification procedures were performed afterwards. Disagreements about study data extraction and quality assessment were resolved by consensus or by discussion with a third party.

Quality of evidence assessment

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[15–17] to assess the quality of evidence of the main outcomes. The quality of evidence was based on the presence of the following: limitations in study design, inconsistencies, indirectness, imprecision of the results, and publication bias. The quality of evidence for the main outcomes was graded as very low, low, moderate, or high.

Statistical analyses

The statistical analyses were performed using the Meta package in R (version 3.4.1). We used relative risk (RR) values and 95% confidence intervals (CIs) as approximations of the outcomes of the included patients. When the 95% CI does not include 1.0, the difference is considered statistically significant. Data with an RR > 1 indicated a high incidence of VTE, DVT and PE. The heterogeneity of the eligible studies was measured using Cochran's Q statistic and the I^2 test. Both $I^2 < 50\%$ and $p > 0.1$ were considered to indicate a low level of heterogeneity. A random-effects model (DerSimonian and Laird method) was applied in the meta-analysis. The funnel plot is a universal method for identifying publication bias; it provides a visual sense of the relationship between effect size and precision. We assessed bias associated with small study size, such as publication bias, using funnel plots by plotting RRs on the vertical axis and comparing them to standard errors on the horizontal axis. We used asymmetry coefficients to assess asymmetry; that is, we examined the difference in unit relative risk increases in the standard error, which is primarily a sample size substitute. Symmetry can be expected if there are no biases associated with small-scale research. For results with significant heterogeneity, we conducted a subgroup analysis to explore sources of heterogeneity, including tumor type, drug type, and surgery. We also performed sensitivity analyses by assessing the effect of removing individual studies on the pooled RR.

Subgroup analyses

We reclassified the included studies and performed subgroup analyses according to the different types of interventions, the different types of cancers or surgeries, the terminal stage of the cancer and whether central venous catheters (CVCs) were used in patients with cancer undergoing chemotherapy. We classified the thromboprophylaxis interventions as LMWH and warfarin, removing a study in which semuloparin was used. In addition, the studies involving mechanical interventions were stratified by type of intervention in a single forest plot. For patients who underwent chemotherapy, we classified the studies into those examining hematological malignancies, lung tumors and abdominal tumors. For patients who underwent surgeries, we classified the studies into those examining gynecologic tumors, brain tumors and abdominal tumors.

Results

Study selection

In total, 13,086 studies were initially returned by the database searches; 12,993 were excluded because they were duplicates, unrelated trials, or non randomized controlled trials (RCTs) or because they involved adult patients without cancer. Therefore, 93 studies were eligible for full text review. Of these, 42 did not meet the inclusion criteria, and 18 did not report the outcomes investigated herein. Finally, 33 studies were included, and their data were included in the meta-analysis. The article selection process is presented in Figure 1.

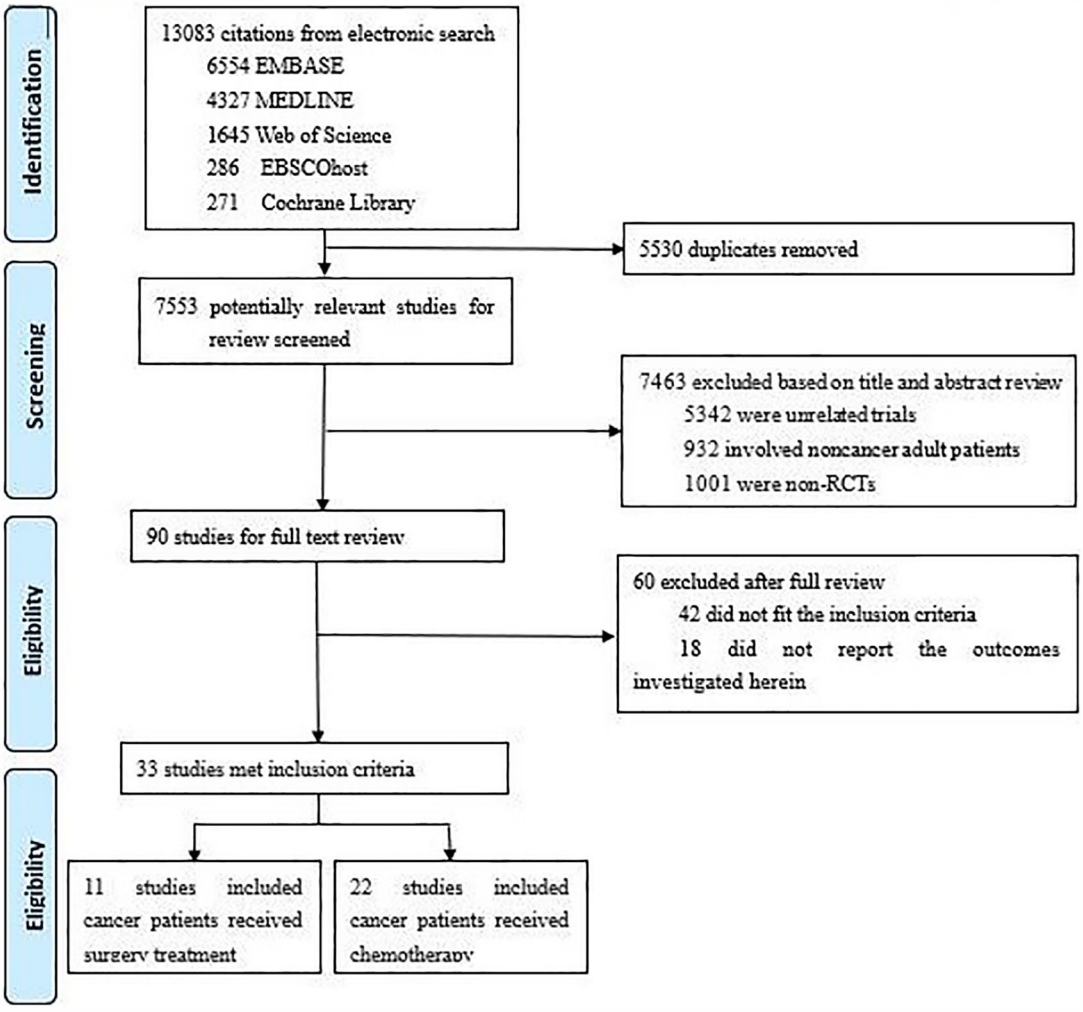

Figure 1. Study selection.
RCT, randomized controlled trial.

Study characteristics

The 33 studies[11,18–49] included a total of 11,942 patients with cancer, of whom 2037 received surgical treatment[11,18–27] and 9950 received chemotherapy.[28–49] We performed meta-analyses stratified by treatment type. The most commonly used prophylactic drugs were heparin or heparin-like compounds, which were used in 16 studies. Overall, five studies used warfarin, and two used mechanical preventive measures as interventions. Only one study used multiple treatments (enoxaparin plus intermittent pneumatic compression) to prevent thrombosis. Mechanical thromboprophylaxis differs from pharmacological thromboprophylaxis with regard to the risk profile of the patient.[50] In addition, from a clinical viewpoint, it does not make sense to include the studies that used mechanical thromboprophylaxis in the surgical group. Therefore, these two studies were not included in the main analyses for each outcome. Instead, we grouped them together in the subgroup analyses. The characteristics of the included trials and the outcomes assessed are summarized in Table 1.

Risk of bias assessment

The risk of bias ratings for the included studies using the Cochrane tool are presented in Figures S1, S2 and Appendix 1. The two abstracts[26,42] included in this report were assessed as having an unclear risk of bias. A total of 18 RCTs were identified with low to moderate levels of risk of bias. We identified 1 trial[43] with a high risk of bias in terms of the sequence generation and 2 trials[46,47] with high levels of risk of bias in terms of the blinding of the outcome assessors. The funnel plots and Egger's regression test for primary and

Table 1. Characteristics of included trials.

First author	Country	Number of patients (*n*)	Cancer	Intervention (*n*)			Placebo	Outpatients/ inpatients
				Drugs or nondrugs	Dosage	Administration		
Bergqvist *et al.*[18]	France	332	Abdominal or pelvic cancer	Enoxaparin	40 mg	s.c. enoxaparin once daily for 19–21 days	Placebo	Inpatients
Cerrato *et al.*[19]	Italy	100	Brain cancer	Calcium heparin	5000 U	Give calcium heparin subcutaneously 2 h before surgery and every 8 h thereafter for at least 7 days.	No thromboprophylaxis	Inpatients
Clarke-Pearson *et al.*[20]	USA	185	Gynecological tumor	Sodium heparin	5000 U	s.c. 2 h preoperatively and every 12 h postoperatively for the first 7 postoperative days.	Placebo	Inpatients
Clarke-Pearson *et al.*[21]	USA	194	Gynecological tumor	Perioperative external pneumatic calf compression	NA	Calf compression continued until discharge from the recovery room or through the first 24 h postoperatively	No thromboprophylaxis	Inpatients
Gondret *et al.*[22]	France	40	Head and neck cancer	Enoxaparin	0.2 ml	Once a day, for 8 days after the operation	Placebo	Inpatients
Kakkar *et al.*[23]	Italy	625	Abdominal or pelvic cancer	Bemiparin	0.2 ml	s.c. injections of bemiparin sodium for 20 ± 2 additional days.	Placebo	Inpatients
Negm *et al.*[24]	Egypt	40	Hepatocellular carcinoma	LMWH enoxaparin	1 IU/kg	Twice daily for 2 weeks from the first day of TACE	No thromboprophylaxis	Inpatients
Perry *et al.*[11]	Canada	186	Malignant glioma	LMWH dalteparin	5000 IU	s.c. once daily	Placebo	Inpatients
Shukla *et al.*[25]	India	99	Colorectal cancer	Dalteparin sodium	2500 IU	s.c. about 2 h before surgery, followed by 2500 IU daily subcutaneously in the morning the prophylaxis was continued until day 6 ± 1.	No thromboprophylaxis	Inpatients
Srikuea *et al.*[26]	Thailand	108	Gynecological and urological cancer	Enoxaparin	0.4 ml	Started after drain removal until 4 weeks postoperatively	No thromboprophylaxis	Outpatients
Turpie *et al.*[27]	Canada	128	Brain cancer	Pneumatic compression	NA	Intermittent calf compression was started during the immediate postoperative period and was continued for a maximum of 5 days	No thromboprophylaxis	Inpatients

(Continued)

Table 1. (Continued)

First author	Country	Number of patients (*n*)	Cancer	Intervention (*n*)			Placebo	Outpatients/ inpatients
				Drugs or nondrugs	Dosage	Administration		
Abdelkefi *et al.*[28]	Tunisia	108	Hematological malignancies	UFH	100 IU/kg/d	Continuous infusion of 100 IU/kg/daily, with a maximal dose of UFH 10,000 IU daily	No thromboprophylaxis	Inpatients
Agnelli *et al.*[29]	Italy	1150	Metastatic or locally advanced solid cancer	Nadroparin	3800 IU	Receive subcutaneous injections of nadroparin once a day. Study treatment was started on the same day as chemotherapy, and was given for the duration of chemotherapy or up to a maximum of 120 days (±10 days).	Placebo	Ambulatory patients
Agnelli *et al.*[30]		3212	Cancer of the lung, pancreas, stomach, colon or rectum, bladder, or ovary	s.c. semuloparin	20 mg	20 mg once daily, or placebo until there was a change of chemotherapy regimen	Placebo	Inpatients
Bern *et al.*[31]	England	87	Colon, breast	Warfarin	1 mg	Warfarin therapy was continued at this dose for 90 days or until there was venogram evidence of thrombosis.	Placebo	Inpatients
Boraks *et al.*[32]	UK	223	Hematological malignancies	Warfarin	1 mg/d	From the time of line insertion until removal	No thromboprophylaxis	Inpatients
Doormaal *et al.*[33]	Italy	498	Hormone-refractory prostate cancer, non-small cell lung cancer IIIB, and locally advanced pancreatic cancer	Nadroparin	50 kg, 3800 IU twice daily; 50–70 kg, 11,400 IU once daily; 70 kg, 15,200 IU once daily	Followed by half-therapeutic doses for an additional 4 weeks (50 kg, 3800 IU once daily; 50–70 kg, 5700 IU once daily; 70 kg, 7600 IU once daily)	No thromboprophylaxis group	Inpatients
Ek *et al.*[34]	Canada, Sweden, Denmark	377	SCLC	Enoxaparin	1 mg/kg	Study drug was started on day 1 of chemotherapy and continued until the 21st day of the last chemotherapy cycle.	No thromboprophylaxis group	Inpatients
Haas *et al.*[35]	Germany, Czech Republic, Ukraine, Romania, and Belarus.	898	Metastatic breast cancer or stage III/IV lung cancer	Certoparin	3000 IU	Once daily for 6 months	Placebo	Inpatients

(Continued)

Table 1. (Continued)

First author	Country	Number of patients (*n*)	Cancer	Intervention (*n*)			Placebo	Outpatients/ inpatients
				Drugs or nondrugs	Dosage	Administration		
Heaton *et al.*[36]	New Zealand	88	Hematological malignancies	Warfarin	NA	Receive either a daily minidose of warfarin	No anticoagulation	Inpatients
Kakkar *et al.*[37]	UK	385	Advanced Cancer	Dalteparin	5000 IU	Receive once-daily s.c. injections of dalteparin	Placebo	Inpatients
Karthaus *et al.*[38]	Germany	439	Cancer	Dalteparin	5000 IU	Within 5–7 days of catheter placement, to receive dalteparin injected subcutaneously once daily.	Placebo	Inpatients
Levine *et al.*[39]	Canada	311	Breast cancer	very-low-dose warfarin	1 mg	Daily for 6 weeks while placebo patients took an identical inert tablet daily	Placebo	Inpatients?
Levine *et al.*[40]	Canada, USA	125	Advanced or metastatic lung, breast, gastrointestinal, bladder, ovarian or prostate cancers, cancer of unknown origin, myeloma or selected lymphomas	Apixaban	5 mg, 10 mg or 20 mg	Once daily of apixaban	Placebo	Inpatients
Maraveyas *et al.*[43]	UK	123	Advanced or metastatic pancreatic cancer	Gemcitabine	1000 mg/m^2	Gemcitabine 1000 mg/m^2 (Burris schedule) for 3 months stratified by extent of disease (LA *versus* M), and KPS (90–100 *versus* 80–60).	No thromboprophylaxis	Inpatients
Maraveyas *et al.*[42]	UK	121	Pancreatic adenocarcinoma	Gemcitabine with weight-adjusted dalteparin	200 IU/kg	Once daily subcutaneously for 4 weeks followed by a step down to 150 IU/kg for a further 8 weeks	Gemcitabine	Inpatients
Monreal *et al.*[41]	Spain	29	Cancer	LMWH	2500 IU s.c.	Once a daily, starting 2 h before insertion of the catheter	No thromboprophylaxis	Inpatients
Niers *et al.*[44]	Netherlands	113	Hematological malignancies	LMWH anti-FXa	2850 U	Started 2 h before insertion of the CVC, and was continued for 3 weeks or until the day of CVC removal	Placebo	Inpatients

(Continued)

Table 1. (Continued)

First author	Country	Number of patients (*n*)	Cancer	Intervention (*n*)			Placebo	Outpatients/ inpatients
				Drugs or nondrugs	Dosage	Administration		
Pelzer *et al.*[45]	Germany	312	Advanced pancreatic cancer	enoxaparin	1 mg/kg	Once daily subcutaneously	Observation group	Outpatients
Young *et al.*[46]	UK	812	Cancer	Warfarin	1 mg/d	From 3 days before CVC insertion. Patients took oral warfarin every day until thrombosis occurred or the catheter had to be removed for any reason and patients were able to temporarily discontinue treatment in the event of thrombocytopenia	No thromboprophylaxis	N/a
Khorana *et al.*[47]	USA	98	Malignancy cancer	Dalteparin	500 units	5000 units s.c. daily or observation for a period of 12 weeks	Observation group	Inpatients
Verso *et al.*[48]	Italy	385	Cancer	Enoxaparin	40 mg	Dose of 40 mg once daily	Placebo	Inpatients
Lecumberri *et al.*[49]	Spain	38	Cancer	Bemiparin	3500 IU	The same first-line therapy + bemiparin 3500 IU subcutaneous daily for 26 weeks (or until disease progression, whatever appeared first), starting the first day of chemotherapy	Chemoradiotherapy	Inpatients

CVC, central venous catheter; LPS, lipopolysaccharide; LA, xxxxxx; LMWH, low-molecular-weight heparin; M, xxxxxxx; N/A, not available; s.c., subcutaneously; SCLC, xxxxxxx; TACE, xxxxxxx; UFH, unfractionated heparin.

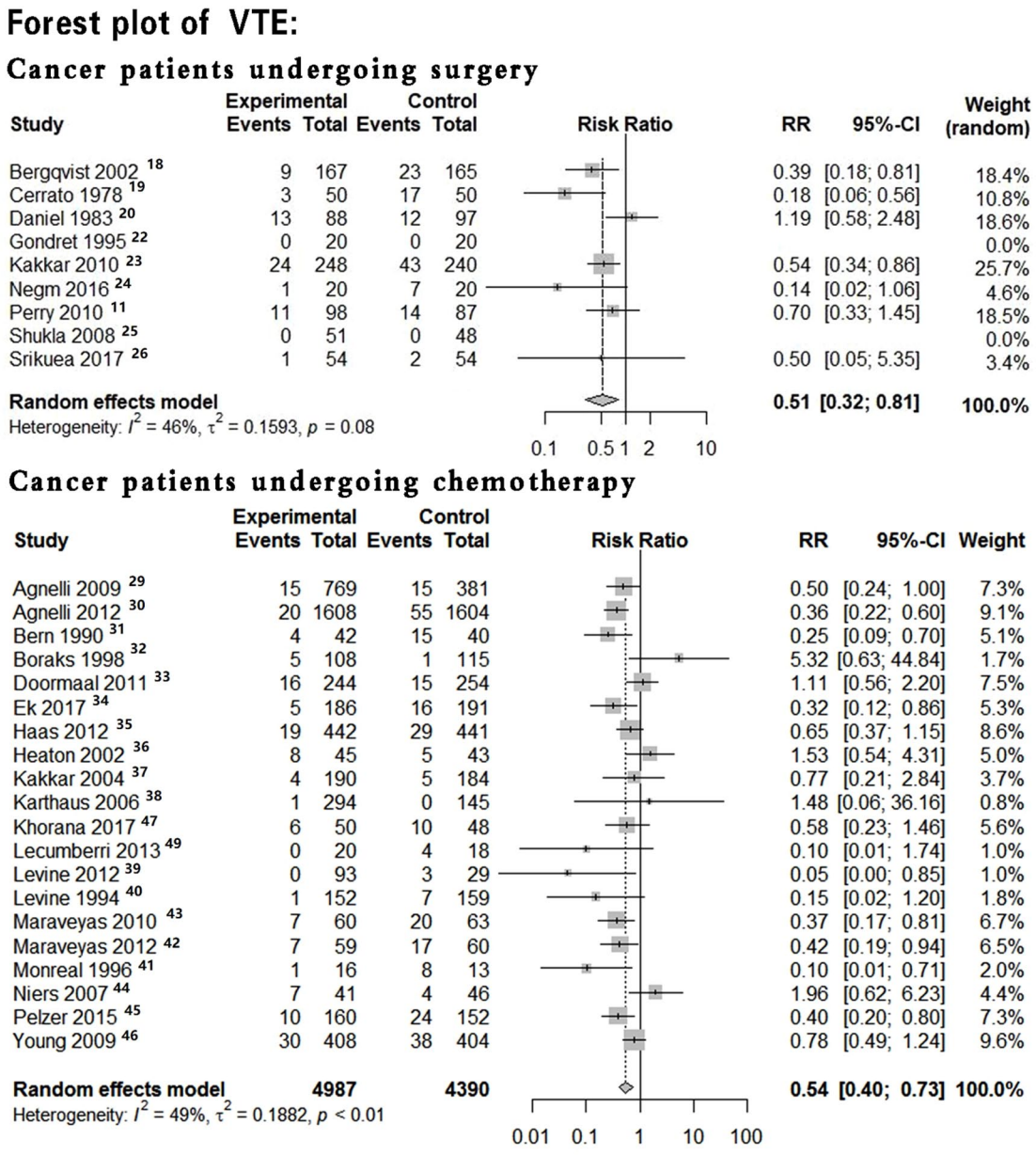

Figure 2. Forest plot of the risk ratio for VTE between thromboprophylaxis and no thromboprophylaxis in patients with cancer undergoing surgery (upper panel) and chemotherapy (lower panel).
CI, confidence interval; RR, relative risk; VTE, venous thromboembolism.

secondary outcomes suggested no statistically significant publication bias. For all-cause mortality in patients undergoing chemotherapy, publication bias was observed. The sensitivity analysis and funnel plots of every outcome are shown in Figures S3–S24.

Primary outcomes

VTE. The primary outcome was the incidence of VTE. A total of 9 trials, including 1577 patients in the surgery group and 20 trials, including 9377 patients in the chemotherapy group were eligible for inclusion in the assessment of this outcome. The results revealed significant differences in VTE between the groups that received prophylaxis and those that did not (RR 0.51, 95% CI 0.32–0.81, $p = 0.0046$, $I^2 = 46.4\%$; RR 0.54, 95% CI 0.4–0.73, $p < 0.0001$, $I^2 = 49\%$, respectively; Figure 2).

DVT. A total of 7 trials, including 1497 patients in the surgery group and 12 trials, including 7751 patients in the chemotherapy group reported data

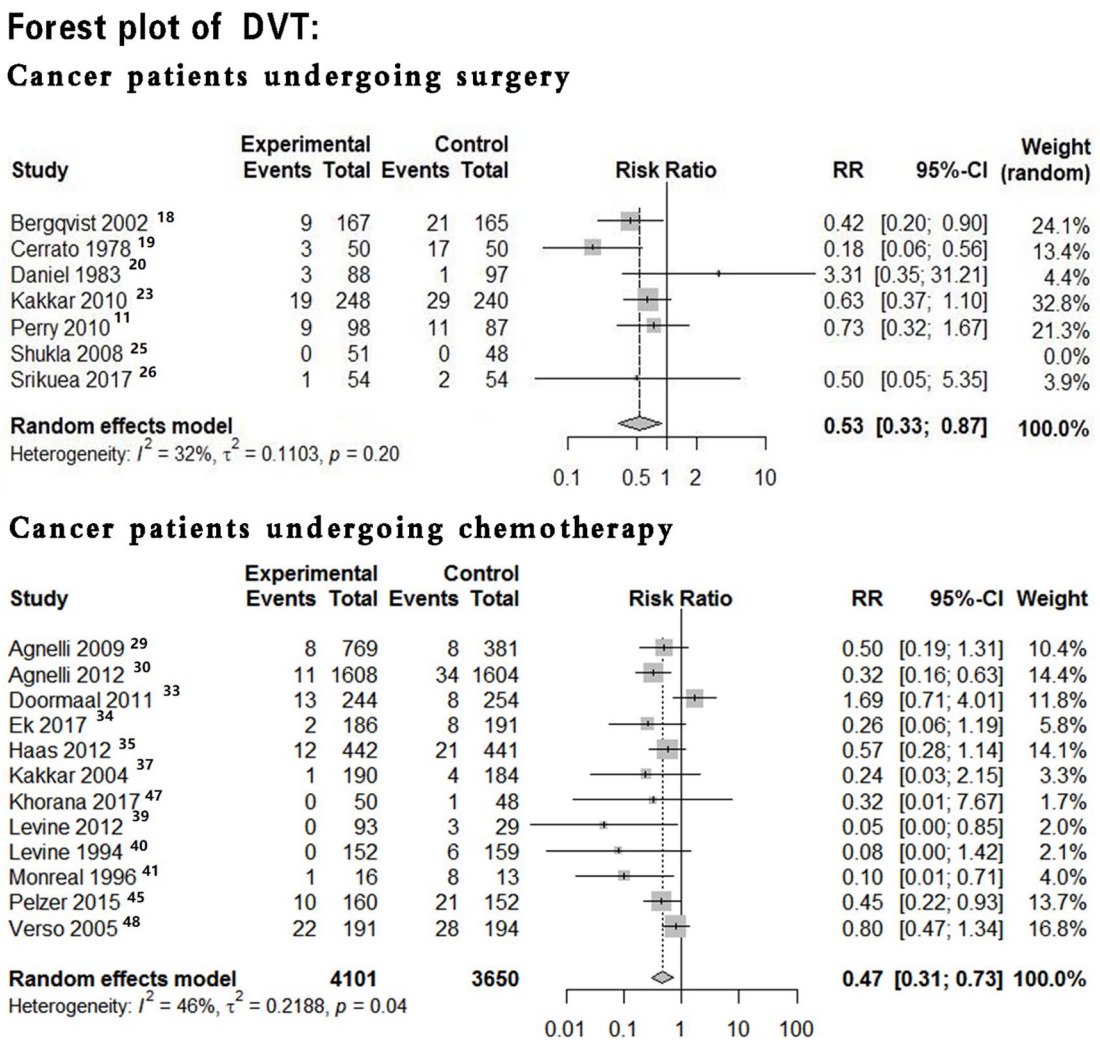

Figure 3. Forest plot of the risk ratio for DVT between thromboprophylaxis and no thromboprophylaxis in patients with cancer undergoing surgery (upper panel) and chemotherapy (lower panel).
CI, confidence interval; DVT, deep vein thrombosis; RR, relative risk.

on DVT events. Significant differences were observed for this outcome between those who received prophylaxis and those who did not (RR 0.53, 95% CI 0.33–0.87, $p = 0.0111$, $I^2 = 31.6\%$; RR 0.47, 95% CI 0.31–0.73, $p = 0.0007$, $I^2 = 46\%$, respectively; Figure 3). The sensitivity analysis showed no substantive differences.

PE. With regard to PE, five trials with 1289 patients in the surgery group showed no significant difference between the prophylaxis and no prophylaxis treatment groups (RR 0.76, 95% CI 0.26–2.19, $p = 0.6105$, $I^2 = 0\%$). In the chemotherapy group, which comprised 11 trials including 7776 patients, the results revealed differences in PE between the prophylaxis and no prophylaxis groups (RR 0.51, 95% CI 0.32–0.81, $p = 0.0048$, $I^2 = 0\%$; Figure 4).

Secondary outcomes

Major bleeding. With regard to major bleeding, the pooled results showed no significant difference between prophylaxis and no prophylaxis in either the surgical or the chemotherapy groups (RR 2.2, 95% CI 0.65–7.39, $p = 0.2036$, $I^2 = 0\%$; RR 1.23, 95% CI 0.87–1.75, $p = 0.2444$, $I^2 = 0\%$, respectively; Figure S25).

All-cause mortality. Thrombus prophylaxis did not result in a statistically significant reduction in all-cause mortality compared with no prophylaxis

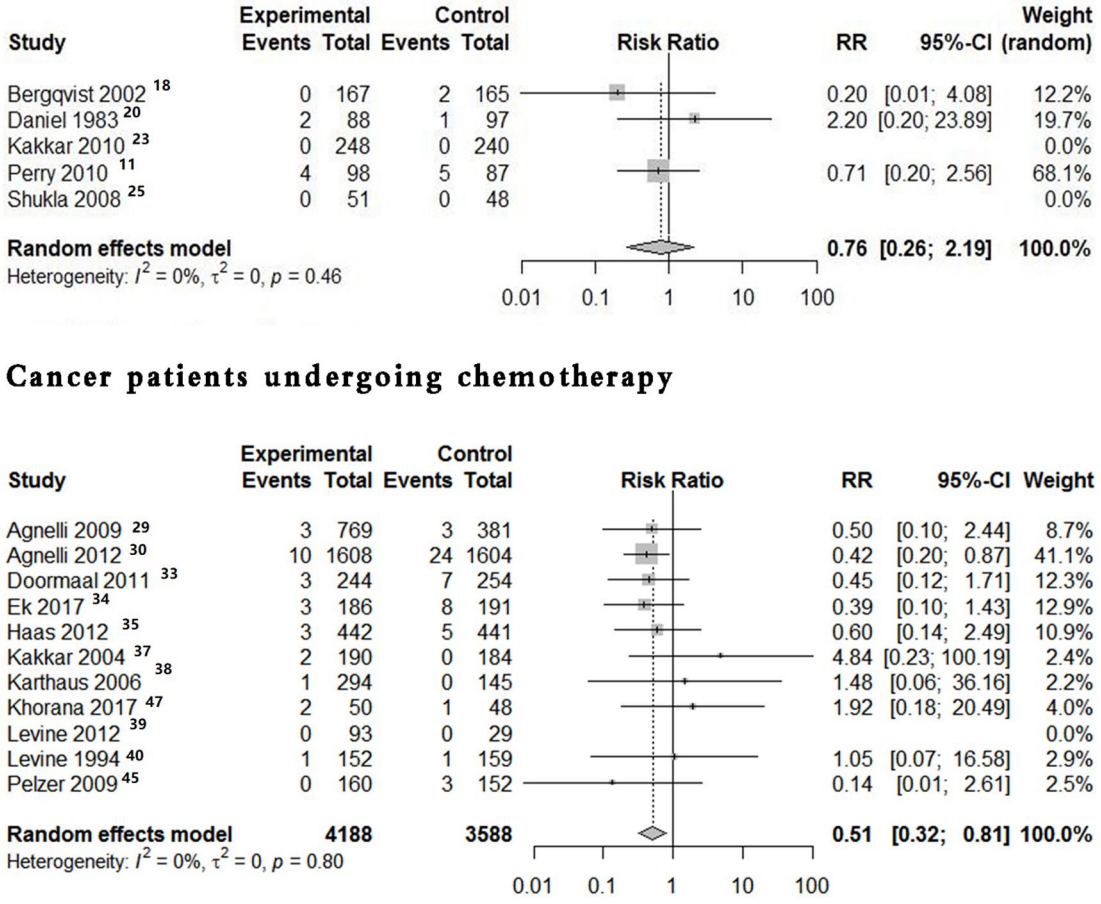

Figure 4. Forest plot of the risk ratio for PE between thromboprophylaxis and no thromboprophylaxis in patients with cancer undergoing surgery (upper panel) and chemotherapy (lower panel).
CI, confidence interval; PE, pulmonary embolism; RR, relative risk.

in either the surgery group or the chemotherapy group (RR 1.18, 95% CI 0.85–1.63, $p = 0.3159$, $I^2 = 0\%$; RR 0.93, 95% CI 0.82–1.05, $p = 0.2461$, $I^2 = 27\%$, respectively; Figure S26).

Thrombocytopenia. Only eight studies, including 2436 patients in the chemotherapy group were eligible for the assessment of this outcome. The results revealed no significant difference in thrombocytopenia between the prophylaxis and no prophylaxis groups (RR 0.94, 95% CI 0.76–1.17, $p = 0.5857$, $I^2 = 0\%$; Figure S27).

Results of subgroup analyses. For patients who underwent chemotherapy using CVCs, there were no significant differences in VTE (RR 0.83, 95% CI 0.39–1.78, $p = 0.01$, $I^2 = 63\%$). After classification according to cancer type, the results showed no difference in VTE between patients with hematological malignancy (RR 1.95, 95% CI 0.94–4.03, $p = 0.58$, $I^2 = 0$) and patients with gynecological tumors (RR 0.85, 95% CI 0.41–1.75, $p = 0.05$, $I^2 = 63\%$; Appendix 2).

Quality of evidence

In patients with cancer who had surgery, the quality of evidence was graded as high for VTE. The quality of evidence for DVT was assessed as moderate because one study identified a high risk of bias in blinding. The quality of evidence for PE and major bleeding was assessed as moderate due to imprecision. The quality of evidence for all-cause mortality was considered to be moderate

because the result crossed the line of no effect and was imprecise, with wide CIs. For the patients who underwent chemotherapy, the evidence regarding VTE, DVT and PE outcomes was of high GRADE quality. The evidence regarding major bleeding was of moderate quality due to the high risk of bias for blinding. The evidence regarding thrombocytopenia was of moderate quality because the 95% CI excluded a RR of 1.0. Due to publication bias and crossing the line of no effect, the evidence related to all-cause mortality was graded as low quality in this group (Table S3).

Discussion

This systematic review and meta-analysis summarizes the evidence concerning the use of thromboprophylaxis in adult patients with cancer, and different types of drug and nondrug thromboprophylaxis treatments are represented. In terms of efficacy, we evaluated the incidence of VTE, DVT and PE in both groups. Statistically significant decreases in VTE and DVT events were found in patients who received thromboprophylaxis compared with those who did not receive thromboprophylaxis. Furthermore, the incidence of PE decreased in patients who underwent chemotherapy. It was important to evaluate the safety of the thromboprophylaxis treatments, so we compared the incidences of major bleeding and thrombocytopenia. There was no significant difference in all-cause mortality between patients who did and did not receive thromboprophylaxis. Thromboprophylaxis did not increase major bleeding events or the incidence of thrombocytopenia.

Thrombosis is a serious complication in cancer and surgical patients, and its prevalence is increasing yearly. The research on thromboprophylaxis has recently been updated. In 2012, Di Nisio and colleagues conducted a study on thromboprophylaxis in outpatient chemotherapy patients and found that anticoagulant drugs reduced the incidence of thrombosis.[51] In 2015, the same conclusion was reached for thoracic and cardiac surgery.[52] The American Society of Clinical Oncology clinical practice guidelines for the treatment and prevention of venous thromboembolism suggest that patients undergoing major cancer surgery should receive preoperative preventive thromboprophylaxis and continue treatment for at least 7–10 days.[53] However, these recommendations were based on older meta-analyses that included only a small number of gynecological and general surgeries.[43–56] Our study included 30 RCTs that were high-quality, large-scale trials in this field and used GRADEpro to assess the methodologic quality of the included studies. Our study adds more credible research evidence to support the guidelines. In 2016, Qiang and colleagues focused on the prevention of thrombosis in perioperative patients with cancer and found that thromboprophylaxis reduced the incidence of VTE to a certain extent but increased the incidence of bleeding.[57] Akl and colleagues analyzed different drugs and reported that LMWH reduced 90-day mortality compared with unfractionated heparin, but neither VTE nor bleeding events showed significant differences according to the drug used.[58] In Brunetti's meta-analysis, direct oral anticoagulants seemed to be as effective and well tolerated as the conventional treatment for the prevention of VTE in patients with cancer in comparison with vitamin-K inhibitors. Higher bleeding rates were found when direct oral anticoagulants were used compared with LMWH.[59] In contrast, although the outcome for VTE in our study was the same as those in the other studies, our meta-analysis was larger than those previously published and included more patients and more interventions. We chose major bleeding rather than all relevant bleeding events as a safety outcome. Major bleeding is a serious adverse clinical event related to hospitalization time and medical expenses.

Because of the varied clinical therapies used, the mechanisms and incidence of thrombosis in patients with cancer undergoing surgery and chemotherapy are significantly different. Patients with cancer undergoing surgery have a VTE risk 2–4 times that of nonsurgical patients with cancer.[60] The reasons for thrombosis in this population are mainly extensive tissue and vascular injury, postoperative tissue factor exposure, procoagulant active cytokine release and postoperative patient activity to reduce blood stasis.[11]

Nonsurgical treatments for cancer, such as chemotherapy, also increase the risk of VTE. Several studies have found that the incidence of VTE in patients with breast cancer treated with chemotherapy drugs increased by 2–5-times compared with the incidence in those not treated with chemotherapy.[61] Chemotherapy can cause vascular endothelial injury, initiate endothelial procoagulant mechanisms, reduce the levels of anticoagulants and increase the levels of type I plasminogen activator inhibitors.[62,63] In addition,

the risk of VTE in chemotherapy patients with long-term use of central venous catheterization is significantly higher than in those without central venous catheterization.[32] Due to the difference between surgical and chemotherapy patients, we analyzed the two groups separately. Our review is the first comprehensive assessment of this issue and is valuable for guiding clinical practice.

While in subgroup analyses, we found that there were no differences in VTE in patients who underwent chemotherapy using CVCs, patients with hematological malignancy and patients with gynecological tumors underwent surgeries. Patients with hematological malignancy often required high-dose chemotherapy, and CVCs were usually used as vascular pathways for delivering chemotherapeutic drugs. In the context of chemotherapy, more RCTs are required to verify the significance of the thrombus prevention effect of thromboprophylaxis in this group of patients. In addition, severe thrombocytopenia may lead to prevention concerns in patients with hematological malignancy.[64] However, for patients with gynecological tumors, preventive measures are recommended because of the high incidence of VTE[65] and low quality of evidence.

We have identified several limitations of this review. First, the outcomes could be biased by the cancer type, etiology and staging. Moreover, the dose of the antithrombosis drug, the administration time and the type of prophylaxis may cause variations in the results. In addition, potential interactions with other drugs used by patients with cancer may alter the concentration of antithrombotic drugs, thereby affecting the occurrence of adverse events.

In summary, this meta-analysis provides evidence that thromboprophylaxis can reduce VTE events (high quality), with no apparent increase in the incidence of major bleeding (moderate quality) in patients with cancer undergoing surgery or chemotherapy. These results provide clinicians with a comprehensive assessment of and high-quality evidence regarding the safety and efficacy of thromboprophylaxis in patients with cancer undergoing surgery or chemotherapy.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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Supplementary material

Supplementary material for this article is available online.

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