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Updated meta-analysis on prevention of venous thromboembolism in ambulatory cancer patients

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Haematologica 2020
Volume 105(3):838-848

ABSTRACT

Randomized clinical trials have evaluated the role of anticoagulants in the prevention of venous thromboembolism (VTE) in ambulatory cancer patients treated with chemotherapy. This meta-analysis is aimed at providing an updated evaluation of the efficacy and safety of anticoagulant prophylaxis in this clinical setting. Medline and Scopus were searched to retrieve randomized controlled trials on the prevention of VTE in ambulatory cancer patients. Two groups of trials were identified with VTE or death as the primary outcome, respectively. VTE was the primary outcome of this analysis. Anticoagulant prophylaxis reduced the incidence of VTE in studies in which the primary outcome was VTE [14 studies, 8,226 patients; odds ratio (OR)=0.45; 95% confidence interval (95% CI): 0.36-0.56] or death (8 studies, 3,727 patients; OR=0.61; 95% CI: 0.47-0.81). When these studies were pooled together, VTE was reduced by 49% (95% CI: 0.43-0.61) with no significant increase in major bleeding (OR=1.30, 95% CI: 0.98-1.73). The risk of major bleeding was increased in studies with VTE as the primary outcome (OR=1.43, 95% CI: 1.01-2.04). Similar reductions of VTE were observed in studies with parenteral (OR=0.43, 95% CI: 0.33-0.56) or oral anticoagulants (OR=0.49, 95% CI: 0.33-0.74). The reduction in VTE was confirmed in patients with lung (OR=0.42, 95% CI: 0.26-0.67) or pancreatic cancer (OR=0.26, 95% CI: 0.14-0.48), in estimated high-risk patients, in high-quality studies and with respect to symptomatic VTE. In conclusion, prophylaxis with oral or parenteral anticoagulants reduces the risk of VTE in ambulatory cancer patients, with an acceptable increase in major bleeding.

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Received: March 7, 2019.

Accepted: June 6, 2019.

Pre-published: June 6, 2019.

doi:10.3324/haematol.2019.221424

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/105/3/838

Introduction

The risk of venous thromboembolism (VTE) is four to seven times higher in patients with cancer than in individuals without this disease.[1,2] The high incidence of cancer-associated thrombosis is probably related to a combination of the intrinsic prothrombotic activity of cancer cells, aggressive chemotherapy treatment, aging of cancer patients, and enhanced VTE detection owing to improvements in imaging technology and frequency of imaging.[3-5] Anti-cancer therapies, either traditional chemotherapy, hormones or biological agents, can potentially increase the risk of VTE up to an annual rate of 15%, depending on the type and combination of agents, or the addition of radiotherapy.[6] Survival of cancer patients has been significantly improved in recent times and this increases the time of risk exposure for VTE in cancer patients.

Based on these epidemiological data, several studies have been conducted aimed at assessing the role of anticoagulants in preventing VTE in ambulatory cancer patients treated with chemotherapy. These studies showed that prophylaxis with anticoagulants reduced the risk of VTE by about 50%, with no significant increase in the risk of major bleeding.[7] However, the use of prophylaxis remains controversial because of concerns over the relatively low incidence of VTE in these patients, the risk-to-benefit ratio, the cost and the inconvenience of prolonged parenteral therapy. As a consequence, antithrombotic prophylaxis is still not recom-

mended in ambulatory cancer patients treated with chemotherapy.[8,9] On this background, the current availability of oral anticoagulants that can be used with no laboratory monitoring reopens the issue of practicality of antithrombotic prophylaxis in ambulatory cancer patients.[10-12] Three clinical trials on the use of new oral anticoagulants for this indication have recently been published.

We performed a meta-analysis of randomized studies to assess the clinical benefit of antithrombotic prophylaxis in ambulatory cancer patients receiving chemotherapy.

Methods

The methods for this meta-analysis are in accordance with "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" (*http://www.prisma-statement.org/*).[13]

Study objectives and outcomes

The primary objective of this meta-analysis of randomized controlled studies was to assess the efficacy of anticoagulant prophylaxis in preventing VTE in ambulatory cancer patients treated with chemotherapy. The secondary objective was to assess the safety of anticoagulant prophylaxis in these patients.

The primary outcome of the study was objectively confirmed VTE, defined as the composite of pulmonary embolism and/or deep vein thrombosis adjudicated according to the criteria and procedures of the individual studies. The secondary outcome was major bleeding defined according to the criteria of the individual studies. Ancillary outcomes were symptomatic VTE and fatal VTE.

Search strategy and study inclusion criteria

We performed unrestricted searches in MEDLINE and Scopus using the terms "cancer AND venous thromboembolism AND prevention" and "cancer AND venous thromboembolism AND prophylaxis". Studies were independently selected by two authors (CB and MV) using predetermined criteria (detaied in the *Online Supplementary Data*).

Randomized controlled trials on the prevention of VTE in ambulatory cancer patients treated with chemotherapy were included in this meta-analysis and results pooled into two groups: (i) studies with VTE as the primary endpoint; and (ii) studies with death as the primary endpoint.

The kappa statistic was used to assess the agreement between reviewers regarding the studies selected.[14]

Statistical analysis

We determined pooled incidences of study outcomes in patients randomized to anticoagulant prophylaxis or no prophylaxis and the pooled odds ratios (OR) with 95% confidence intervals (95% CI). We planned cumulative and separate analyses for studies with VTE or mortality as the primary outcome.

Sensitivity analyses were performed concerning (i) parenteral or oral anticoagulants; (ii) symptomatic VTE; (iii) fatal VTE; (iv) subgroups of patients based on the primary cancer site (lung, pancreas and breast); (v) patients considered as being at high-risk of VTE; and (vi) high-quality studies.

Study quality was evaluated using the Jadad score and the Cochrane risk assessment tool.[15]

Data were pooled by the Mantel-Haenszel method;[16] results are reported according to a fixed-effects model in the absence of significant heterogeneity and to a random-effects model in the presence of significant heterogeneity.[17,18] The Cochran χ^2 test and the I^2 test for heterogeneity were used to assess between-study heterogeneity.[16,17] Significant heterogeneity was considered present at $P<0.10$ and $I^2>50\%$.[18]

Correction for zero cells was performed. Publication bias was assessed visually by the use of funnel plots.

Statistical analyses were conducted using Review Manager release 5.3 (The Cochrane Collaboration, Oxford, England) and StatsDirect 3.0.

Results

Overall, 22 papers were found reporting on 23 studies fulfilling the inclusion criteria (flow diagram in *Online Supplementary Figure S1*).[11-12,19-38] After discussion among the authors, a randomized double-blind phase II study with apixaban compared to placebo was included in the analysis despite the main outcome being major bleeding.[10] The reasons for inclusion were high-quality, appropriate study population and the potential to increase the power of the meta-analysis with respect to the efficacy and safety of oral anticoagulants. The main features of included studies are reported in Tables 1 and 2. The primary outcome was VTE in 16 studies and death in eight. The agreement between reviewers regarding study selection was good (kappa statistic: 0.88).

Among the 15 studies with VTE as the primary outcome, eight were double-blind studies with placebo as the comparator.[10-12,19,21-22,24-25] In five studies the comparator was no treatment and in one it was aspirin. One paper was composed of two 'twin-studies', one including patients with breast cancer and the other including patients with lung cancer. With regards to the study populations, these were limited to patients with a single primary site of cancer in eight studies (breast and pancreas in two studies each,[19,24,26-27] acute lymphatic leukemia,[20] multiple myeloma,[23] glioma[22] and lung[24] cancer in one study each) while multiple cancers were included in seven studies. In three studies patients were eligible in the case of an estimated increased risk for VTE assessed by the Khorana score.[11-12,29] The number of study patients varied from a minimum of 34 to a maximum of 3,212. Asymptomatic or incidental VTE accounted for a study outcome event in nine studies.[11-12,24-26,29] All but one of the studies were conducted in adult patients. A systematic assessment of thrombosis by screening tests was scheduled in three studies[12,20,29] and was aimed at the diagnosis of lower limb deep vein thrombosis in two studies and to assess upper-body and cerebral vein thrombosis in one study (Table 1).

Among the studies with death as the primary outcome,[30-38] two were double-blind studies with placebo as the comparator. In seven studies the comparator was no treatment. Patients were eligible in the case of a diagnosis of advanced cancer in four studies.[31,33-34,36] No systematic assessment of thrombosis was scheduled (Table 1).

According to the Jadad scale, nine studies[10-12,19,21-22,24-25] were classified as good quality (*Onlne Supplementary Table S1*).

Efficacy of anticoagulant prophylaxis

In the 14 studies with VTE as the primary outcome and data available for the efficacy analysis (8,226 patients), the pooled incidence of symptomatic or asymptomatic (incidental) VTE was 2% in patients randomized to anticoagulant prophylaxis (95% CI: 2-3; I^2=85%) and 6% in

patients not randomized to anticoagulant prophylaxis (95% CI: 5-7; I^2=91%). In these studies, anticoagulant prophylaxis reduced the incidence of VTE (OR=0.45, 95% CI: 0.36-0.56; I^2=5%) (Figure 1).

Among studies with VTE as the primary outcome, prophylaxis with parenteral anticoagulants (11 studies, 6,700 patients; OR=0.43, 95% CI: 0.33-0.56; I^2=0%) and oral agents (3 studies, 1,526 patients; OR=0.49, 95% CI: 0.33-0.74; I^2=57%) was associated with the same magnitude of reduction of VTE risk. However, significant heterogeneity

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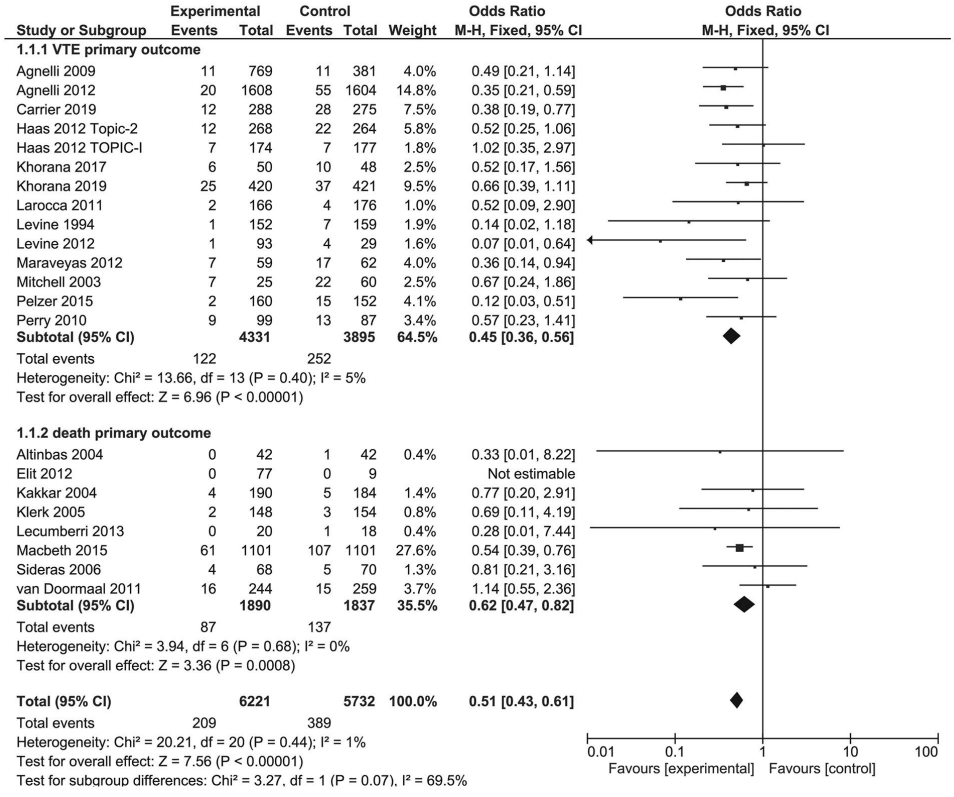

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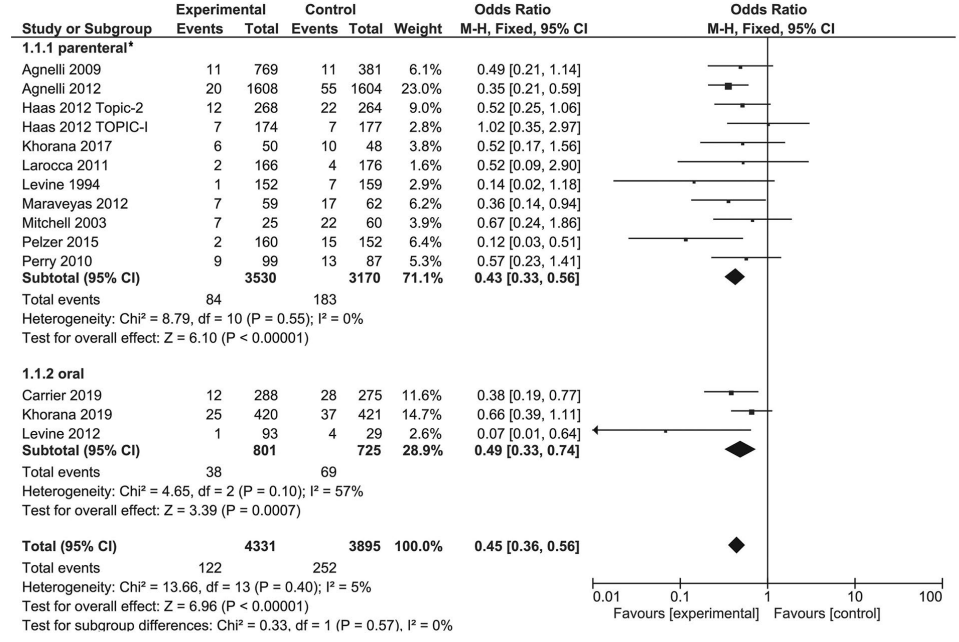

Figure 1. Efficacy of anticoagulant prophylaxis for the prevention of venous thromboembolism in ambulatory cancer patients receiving chemotherapy. (A) Analysis of studies having venous thromboembolism or death as the primary outcome. (B) Analysis of studies with parenteral or oral anticoagulants. *Warfarin was used for prophyaxis in one study.[19]

Table 1. Main features of randomized studies on the role of anticoagulants in ambulatory cancer patients receiving chemotherapy with VTE as primary outcome.

Author, year	D-B patients	N. of	Eligible cancers	Main inclusion criteria	Study treatments	Primary outcome of prophylaxis	Duration
Levine, 1994[19]	Yes	311	Metastatic breast carcinoma	First-line or second-line CHT for 4 weeks or less	Warfarin (INR 1.3-1.9) *vs.* Placebo	DVT or PE and arterial thrombosis (myocardial infarction, stroke, or peripheral-artery thrombosis)	6 weeks
Mitchell, 2003[20]	No	85	Newly diagnosed acute lymphoblastic leukemia	Age >6 months and <18 years, at the beginning of the induction CHT, a functioning CVL placed <2 weeks of initiating induction CHT	Antithrombin (plasma levels 3.0 - 4.0 U/mL) *vs.* No antithrombin	Clinically symptomatic or asymptomatic TE in any location. TE categorized as not clinically significant or clinically significant	4 weeks
Agnelli, 2009[21]	Yes	1150	Metastatic or locally advanced lung, GI, pancreatic, breast, ovarian, or head and neck cancer	Receiving CHT, age> 18 years	Nadroparin (3800 IU o.d.) *vs.* Placebo	Composite of symptomatic venous or arterial TE	For the duration of CHT (maximum 120 ±10 days)
Perry, 2010[22]	Yes	186	Newly diagnosed, pathologically confirmed WHO grade 3 or grade 4 glioma	Age >18 years	Dalteparin (5000 IU o.d.) *vs.* Placebo	Symptomatic DVT or PE	6 months
Larocca, 2011[23]	No	342	Newly diagnosed multiple myeloma	Previously untreated patients; age >18 and <65 years	Enoxaparin (40 mg o.d.) *vs.* ASA (100 mg o.d.)	First objectively confirmed symptomatic DVT, PE, arterial thrombosis, any acute cardiovascular event or sudden, otherwise unexplained death	During the 4 cycles of Rd therapy and the 6 cycles of MPR consolidation
Haas, TOPIC-1 2012[24]	Yes	351	Objectively proven, disseminated metastatic breast carcinoma	Adult patients receiving first- or second-line CHT	Certoparin (3000 IU o.d.) *vs.* Placebo	First objectively confirmed symptomatic or asymptomatic DVT, symptomatic PE, thrombosis of the jugular or subclavian veins; and superficial thrombophlebitis	6 months
Haas, TOPIC-2 2012[24]	Yes	532	Objectively proven, stage III or IV, non-small cell lung carcinoma	Adult patients receiving first- or second-line CHT	Certoparin (3000 IU o.d.) *vs.* Placebo	First objectively confirmed symptomatic or asymptomatic DVT, symptomatic PE, thrombosis of the jugular or subclavian veins; and superficial thrombophlebitis	6 months
Agnelli, 2012[25]	Yes	3212	Metastatic or locally advanced cancer of the lung, pancreas, stomach, colon or rectum, bladder, and ovary	Patients >18 years of age and planned to receive a course of CHT	Semuloparin (20 mg o.d.) *vs.* Placebo	Any symptomatic DVT in lower or upper limbs, any non-fatal PE, or death related to VTE (fatal PE or unexplained death)	3 months, then discontinued when CHT was stopped or regimen changed
Maraveyas, 2012[26]	No	121	Non-resectable, recurrent or metastatic pancreatic adenocarcinoma(histological or cytological diagnosis)	Age >18 years, life expectancy >12 weeks, KPS of 60%; evaluable disease in baseline CT, adequate hematologic function, and bilirubin <1.5 UNL	Dalteparin (200 IU/Kg o.d. for 4 weeks then 150 IU/Kg) *vs.* No prophylaxis	All types of DVT/PE, all arterial events and all visceral TE	12 weeks
Levine, 2012[10]	Yes	122	Advanced or metastatic lung, breast, colon, rectum, pancreas, stomach, bladder, cancer of unknown origin, ovarian or prostate cancer, myeloma or selected lymphomas	Receiving first-line or second-line CHT; able to begin study medication within 6 weeks of starting CHT; expected course of CHT >90 days; age > 18 years.	Apixaban (5mg, 10 mg or 20 mg o.d.) *vs.* Placebo	Major bleeding event or a clinically relevant non-major bleeding event	12 weeks
Pelzer, 2015[27]	No	312	Histologically confirmed advanced pancreatic cancer	No previous RT or CHT, KPS of 60%, measurable tumor lesion confirmed by CT or MR <14 days, age >18 years	Enoxaparin (40 mg o.d.) *vs.* No prophylaxis	First symptomatic VTE	Until disease progression *
Zwicker, 2015[28]	No	34	Adenocarcinoma of pancreas (locally advanced or metastatic), or stomach (unresectable or metastatic), colorectal stage IV, non-small cell lung cancer stage III or IV, relapsed or stage IV ovarian	Histologically confirmed malignancy with no curative therapies, <4 weeks of first or second line CHT, life expectancy >6 months, ECOG ≤ 2; neutrophil count ≥1.0×10^9, platelet count ≥100×10^9/L	Enoxaparin (40 mg o.d.) *vs.* No enoxaparin	Symptomatic or proximal VTE, based on levels of tissue factor-bearing microparticles	60-day

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Author, year	D-B	N. of patients	Eligible cancers	Main inclusion criteria	Study treatments	Primary outcome	Duration of prophylaxis
Khorana, 2017[29]	No	98	Lung, stomach, pancreas, lymphoma, gynecological, genitourinary (excluding prostate)	Histological diagnosis of malignancy, planned initiation of a new systemic CHT regimen (either initial or after progression on CHT), age ≥18 years	Dalteparin (5000 IU o.d.) *vs.* No dalteparin	Symptomatic lower extremity DVT, PE and upper extremity thrombosis, unsuspected DVT and PE detected by lower extremity ultrasonography and CT	12 weeks
Khorana, 2019*[11]	Yes	809	Solid tumor or lymphoma	Age >18 years, Khorana score >2, expected survival >6 months, plan to start a new systemic regimen within 1 week	Rivaroxaban (10 mg o.d.) *vs.* Placebo	Objectively confirmed symptomatic or asymptomatic lower-extremity proximal DVT, symptomatic upper-extremity or distal lower-extremity DVT, symptomatic or incidental PE and VTE–related death	180 (± 3) days
Carrier, 2019[12]	Yes	563	Newly diagnosed cancer or progression of known cancer after complete or partial remission	Initiating a new course of CHT with a minimum treatment intent of 3 months, Khorana score >2, age >18 years	Apixaban (2.5 mg t.d.) *vs.* Placebo	First objectively documented symptomatic or incidentally detected proximal DVT of the lower or upper limbs, any nonfatal symptomatic or incidental PE, and PE–related death	180 days

Enrolled patients underwent bilateral lower-extremity venous duplex compression ultrasonography to exclude pre-existing proximal deep-vein thrombosis based on prior studies in high-risk patients demonstrating a high rate of baseline thrombosis for which prophylactic anticoagulation would be inadequate. CHT: chemotherapy; INR: International Normalized Ratio; DVT: deep vein thrombosis; PE: pulmonary embolism; CVL: central venous line; TE: thromboembolism; GI: gastrointenstinal; IU: international units; o.d.: once daily; WHO: World Health Organization; ASA: acetylsalicylic acid; Rd: induction with lenalidomide plus low-dose dexamethasone; MPR: melphalan–prednisone-lenalidomide; VTE: venous thromboembolism; KPS: Karnofsky performance status scale; CT: computed tomography; UNL: upper normal limit; RT: radiotherapy; MR: magnetic resonance; ECOG= Eastern Cooperative Oncology Group; t.d.: twice daily..

was found in the analysis of studies with oral agents, which disappeared after the removal of a dose-ranging study from the analysis.

Anticoagulant prophylaxis reduced symptomatic VTE (OR=0.48, 95% CI: 0.39-0.60) but not fatal VTE (OR=0.52, 95% CI: 0.25-1.08) in studies with VTE as the primary outcome (Table 3; Figure 2).

In the eight studies with death as the primary endpoint, prophylaxis was associated with a reduction of VTE (8 studies, 3,727 patients; OR=0.61, 95% CI: 0.47-0.81; I^2=0%)

When all studies were pooled in a single analysis, anticoagulant prophylaxis was confirmed to reduce the incidence of VTE (22 studies, 11,953 patients; OR=0.51, 95% CI: 0.43-0.61; I^2=2.4%) (Figure 1) and of symptomatic VTE (17 studies, 10,374 patients; OR=0.49, 95% CI: 0.39-0.61; I^2= 0%) with no heterogeneity (Figure 2).

The reduction in the incidence of VTE with the use of anticoagulant prophylaxis was confirmed in patients with lung cancer (3 studies, 1,991 patients; OR=0.42, 95% CI: 0.26-0.67; I^2=0%), pancreatic cancer (4 studies, 740 patients; OR=0.26; 95% CI: 0.14-0.48; I^2=21%), in patients at estimated high risk according to the Khorana score (5 studies, 2,167 patients; OR=0.48; 95% CI: 0.34-0.68; I^2=0%) and in high-quality studies (OR=0.47, 95% CI: 0.36-0.60), all from studies with VTE as the primary outcome (Table 3, Figure 3).

No evidence of publication bias was found in individual comparisons at visual inspection of funnel plots.

Safety of anticoagulant prophylaxis

For the analysis of safety, the results from studies with VTE or death as the primary outcome were pooled in a single analysis. Overall, 24 studies reported on the incidence of major bleeding in patients randomized to anticoagulant prophylaxis or no prophylaxis. The pooled incidence of major bleeding was 2% in patients randomized to prophylaxis or to no prophylaxis, with significant heterogeneity (95% CI: 0.17-0.31; I^2>50%). Heterogeneity persisted after removal of outlier studies and disappeared when the analysis was limited to high-quality studies.

Anticoagulant prophylaxis was not associated with an increase in the risk of major bleeding (24 studies, 12,014 patients; OR=1.30, 95% CI: 0.98-1.73; I^2=0%) (Figure 4). Similar results were obtained in studies with parenteral anticoagulants (21 studies, 10,713 patients; OR=1.27, 95% CI: 0.93-1.73; I2=0%) or oral anticoagulants (3 studies, 1,494 patients; OR=1.78, 95% CI: 0.83-3.83; I^2=0%).

When the analysis was limited to high-quality studies or those with VTE as the primary outcome, the use of anticoagulant prophylaxis was associated with a marginally significant increase in major bleeding (Table 3).

Discussion

This meta-analysis in ambulatory cancer patients treated with chemotherapy shows that anticoagulant prophylaxis, with either oral or parenteral agents, is associated with a 50% reduction in the incidence of VTE and no significant increase in major bleeding. The efficacy of prophylaxis in reducing VTE was consistent in studies with VTE or death as the primary outcome and in all sensitivity analyses.

Anticoagulant prophylaxis is currently used to prevent VTE in patients undergoing major cancer surgery as well as in cancer patients admitted to hospital for an acute illness.[40] Despite the results of individual studies and previous meta-analyses, antithrombotic prophylaxis remained controversial and is still not recommended in ambulatory cancer patients treated with chemotherapy.[8,9] The main concerns regarding the use of antithrombotic prophylaxis

Table 2. Main features of randomized studies on the role of anticoagulants in ambulatory cancer patients receiving chemotherapy with death as the primary outcome.

Author, year	D-B	N. of patients	Main inclusion criteria	Experimental	Duration of follow-up	Duration of prophylaxis	Definition of major bleeding	Study completed
Labeau, 1994[30]	No	277	SCLC	Heparin calcium (initially 500 IU/kg/day then adjusted by clotting times 2-3 times normal value) t.d. (70 patients) or t.i.d. (62 patients) times daily *vs.* No heparin	from randomization to the sixth course of CHT	5 weeks (with 1week stop after the second course of CHT)	Not reported	Yes
Kakkar, 2004[31]	Yes	374	Advanced stage III or IV (locally advanced or metastatic) cancer* of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary, or uterus; age between 18 and 80 years.	Dalteparin (5,000 IU o.d.) *vs.* Placebo	1 year	1 year or until death	According to standard criteria[39]	Yes
Altinbas, 2004[32]	No	84	SCLC* , ECOG PS < 3; age between 18 and 75 years.	Dalteparin, (5,000 IU o.d.) *vs.* No dalteparin	1 year	18 weeks	Not specified	Yes
Klerk, 2005[33]	Yes	302	Adult patients with metastatic or locally advanced solid tumors*	Nadroparin (BW adjusted**, t.d. during the initial 14 days and o.d. thereafter for another 4 weeks) vs Placebo.	6 weeks	6 weeks	Clinically overt associated with hemoglobin decrease >2 g/dL, requiring >2 transfusion, or retroperitoneal or intracranial.	Yes
Sideras, 2006[34]	Yes	138	Advanced breast cancer failed first-line chemotherapy, advanced prostate cancer failed primary hormonal therapy, advanced lung cancer, or advanced colorectal. ECOG PS <2, life expectancy >12 weeks, age >18 years	Dalteparin (5,000IU o.d.) *vs.* Placebo	13 months	2 years	Not specified	Stopped after first interim analysis
van Doormaal, 2011[35]	No	503	Prostate cancer* <6 m after diagnosis of hormone-refractory state, NSCLC* without clinically significant pleural effusion <3 m after diagnosis of stage IIIB, or locally advanced pancreatic cancer* <3 m after diagnosis	Nadroparin (BW-adjusted therapeutic dose for 2 weeks, and 4 weeks at half therapeutic dose) *vs.* No nadroparin	46 weeks	46 weeks	Overt with hemoglobin decrease >2 g/dL or transfusion >2 units.	Yes
Elit, 2012[36]	No	86	FIGO stage IIB to IV epithelial ovarian cancer*, primary peritoneal or Fallopiantube cancer*; age between 18 and 75 years	Dalteparin (50 IU/kg, 100 IU/kg, or 150 IU/kg) *vs.* No dalteparin	Six 21-day cycles	Within 7 days prior to the cycle 1 of CHT to day 21 of cycle 3	Not specified	Premature interruption slow recruitment
Lecumberri, 2013[37]	No	38	Limited stage SCLC*, ECOG PS ≤2, platelets >100,000/mm^3 and absence of active bleeding; age >18 years.	bemiparin (3,500 IU/day) *vs.* No bemiparin	12 months	26 weeks	Associated with hemoglobin decrease >2 g/dL, or transfusion >2 units, involved a critical site, contributed to death, or any clinically relevant bleeding requiring the stop of treatment	Premature interruption slow recruitment
Macbeth, 2015[38]	No	2202	SCLC or NSCLC* <6 weeks of diagnosis; age 18 years or older; ECOG-PS 0-3; able to self-administer LMWH or have it administered to them by a caregiver.	Deltaparin (5,000 IU/day) *vs.* No dalteparin	1 year	24 weeks	Associated with death, occurred at a critical site or resulted in transfusion >2 units, or hemoglobin decrease >2.0 g/dL	The trial did not reach the intended number of outcome events

SCLC: small cell lung cancer; IU: International Units; t.d.: twice daily; t.i.d.:.*ter in die*; CHT: chemotherapy; o.d.: once daily; ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; BW: body weight; NSCLC: non-small cell lung cancer; FIGO: International Federation of Gynecology and Obstetrics; LMWH: low molecular weight heparin. * histologically confirmed; **0.4 mL if body weight <50 kg, 0.6 mL if body weight between 50 and 70 kg, and 0.8 mL if body weight > 70 kg. ° defined according to GCIG-CA125 response criteria.

Table 3. Results of sensitivity analyses.

Sensitivity analyses of efficacy	N of studies; n of patients	OR	95% CI	I²
Symptomatic VTE	12 studies; 7,578 patients	0.48	0.39 -0.60	0%
Fatal VTE	6 studies; 4,705 patients	0.52*	0.25 -1.08	0%
High-risk patients	5 studies**; 2,167 patients	0.48	0.34-0.68	0%
High-quality studies[10-12,19,21-22,24-25]	9 studies; 7,268 patients	0.47	0.36-0.60	15%
Sensitivity analyses of safety	**N of studies; n of patients**	**OR***	**95% CI**	**I squared**
Parenteral anticoagulants[19,21-22,24-25]	21 studies; 10,488 patients	1.27	0.93-1.73	0%
Oral anticoagulants[10-12]	3 studies; 1,526 patients	1.78	0.83-3.83	0%
High-quality studies[10-12,19,21-22,24-25]	9 studies; 7,268 patients	1.50	1.00-2.25	0%
VTE as primary outcome	15 studies; 8,258 patients	1.43	1.01-2.04	0%
Death as primary outcome	9 studies; 4,004 patients	1.16	0.70-1.92	0%

*after correction for zero cells. **This analysis included three studies in full and the subgroups of patients estimated to be at high risk of venous thromboembolism from two additional studies. OR: odds ratio; 95% CI: 95% confidence interval; VTE: venous thromboembolism.

for this specific indication were firstly the relatively low incidence of VTE in these patients. In our analysis, the incidence of VTE in studies in ambulatory cancer patients treated with chemotherapy varied from 2.3% to over 30% without anticoagulant prophylaxis. Such a huge variation is probably related to different study designs concerning populations (single primary site of cancer vs. multiple sites, high risk for VTE *vs*. all-comers), anticancer therapies (asparaginase *vs*. others, old *vs*. new regimens) and methods for VTE detection (screening *vs*. symptomatic events). In clinical practice, this heterogeneity is perceived by clinicians as uncertainty concerning the actual need for prophylaxis of VTE in each individual cancer patient. In fact, the risk of VTE correlates with the type of solid or hematologic cancer, the presence of metastatic disease, the use of chemotherapy or radiotherapy, surgery or hospitalization and, according to more recent research, to genetic cancer rearrangements (*ALK* and *ROS1* in lung cancer).[41-43] A clinical model was proposed to categorize ambulatory cancer patients treated with chemotherapy according to their risk of VTE.[44] A meta-analysis of 55 cohorts (34,555 ambulatory cancer patients) recently showed that although this model is able to identify categories of patients at different risk of VTE, most VTE events occur outside the high-risk group.[45] Further studies should be performed to improve the selection of ambulatory cancer patients who are candidates for anticoagulant prophylaxis. Personalized medicine and big data technology could have a role in this process.

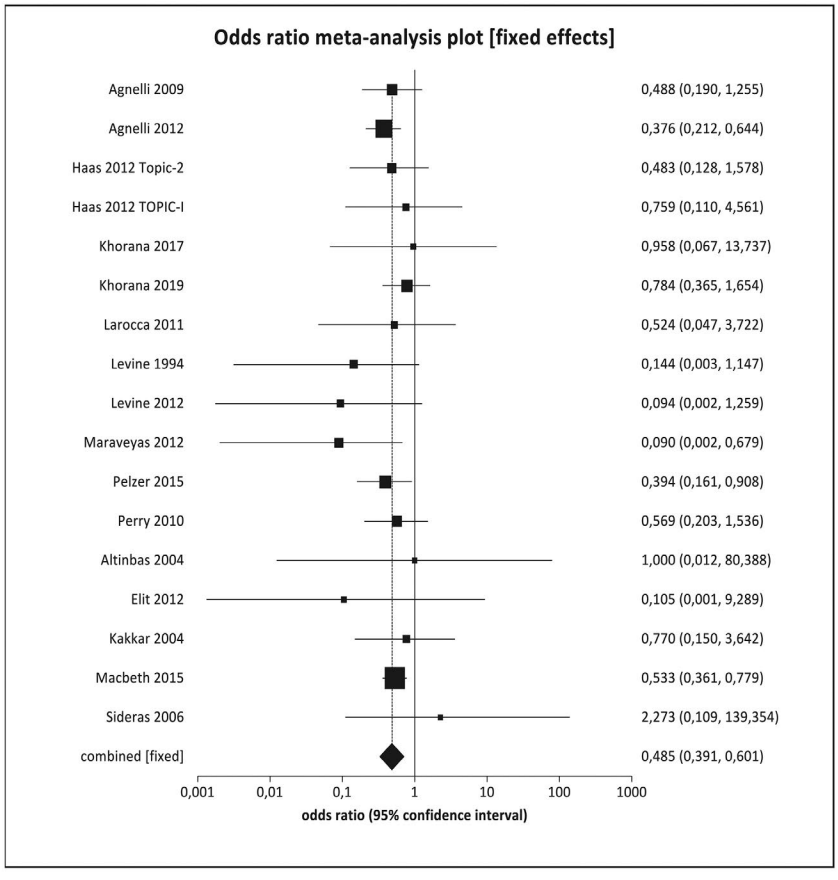
The second concern about the use of prophylaxis in cancer patients treated with chemotherapy is the inconvenience of prolonged parenteral therapy. A not negligible number of patients in the context of the selected clinical studies discontinued anticoagulant prophylaxis for reasons other than thrombosis or bleeding (about 30%). Hence, it may be problematic for large numbers of patients to tolerate longer durations of prophylaxis. In this scenario, the availability of oral anticoagulants that can be used with no laboratory monitoring and with the potential for few drug-drug interactions could solve at least the issue of parenteral administration and make prophylaxis acceptable also for extended periods. Three randomized studies have assessed the efficacy and safety of apixaban (2 studies)[10-11] and rivaroxaban (1 study)[12] for the prevention of VTE in cancer patients and provided promising results. In particular, our meta-analysis found similar risk reductions with parenteral or oral agents. Direct oral anticoagulants could make prophylaxis feasible for ambulatory cancer patients receiving chemotherapy as they will be more acceptable than parenteral agents for those at high risk of VTE.

An additional concern regards the risk-to-benefit ratio of anticoagulant prophylaxis. The pooled incidence of major bleeding was 2% in patients randomized to anticoagulant prophylaxis, with high variability across individual studies as shown by significant heterogeneity. Differences in study populations across individual studies could have had a major role as determinants of heterogeneity. No significant increase in the risk of major bleeding in patients randomized to receive anticoagulant prophylaxis, compared to the risk in controls, was found in this meta-analysis when all studies were pooled together. This finding is reassuring as cancer patients are known to have an increased risk of bleeding, mainly related to the primary site of the cancer, the need for invasive procedures and thrombocytopenia. However, the analysis on risk of major bleeding in high-quality studies and that in studies with VTE as the primary outcome showed a marginally significant increase in the risk of major bleeding by about 50%. Additional evidence on risk factors for major bleeding in ambulatory cancer patients receiving chemotherapy could help decision-making concerning the use of prophylaxis.

Fatal VTE was not significantly reduced by anticoagulant prophylaxis. This result should be considered taking into account the low rates of death deemed to be due to VTE in patients with advanced cancer. Indeed, previous studies failed to show an effect of heparin, given at either therapeutic or prophylactic doses, in improving survival in cancer patients. However, it should be taken into account that a diagnosis of new VTE in cancer patients may affect quality of life and lead to the interruption of anticancer treatment. In this view, preventing VTE can be a relevant clinical goal.

Among the sensitivity analyses, we included one on patients at 'high-risk' of VTE, which confirmed the efficacy of anticoagulant prophylaxis in this setting. The Khorana score was used to identify this population of

A



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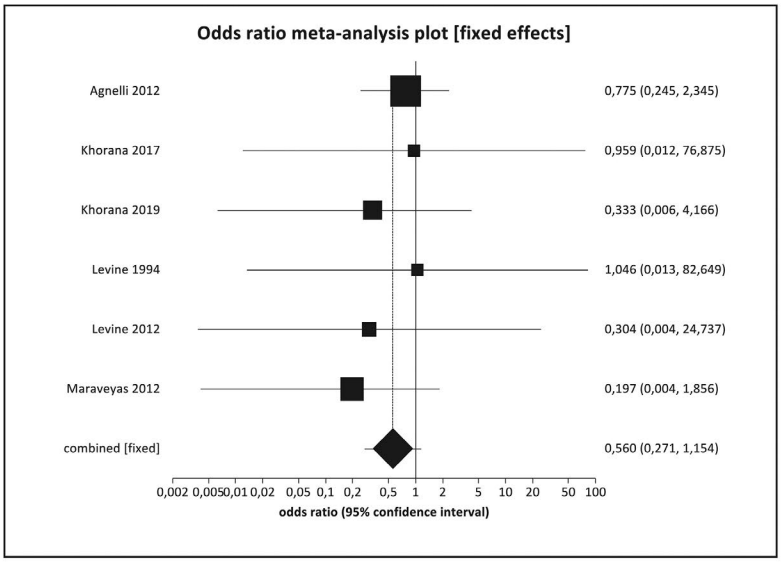

Figure 2. Efficacy of anticoagulant prophylaxis for the prevention of venous thromboembolism (VTE) in ambulatory cancer patients receiving chemotherapy in studies with VTE as the primary outcome. (A) Efficacy for the prevention of symptomatic VTE. (B) Efficacy for the prevention of fatal VTE.

patients.[44] Even though no consensus exists on the optimal strategy to identify ambulatory cancer patients at high risk of a first VTE,[45] the Khorana approach was followed in the two recent studies.[11,12] While the efficacy of anticoagulant prophylaxis was confirmed in this analysis, the incidence of VTE in the placebo arms in these two trials was 10%. Whether this incidence is high enough to recommend anticoagulant prophylaxis is controversial.

Our study has several limitations in addition to those intrinsic to a meta-analytic approach, which combines heterogeneous datasets. For example, the heterogeneity in the incidence of VTE was not resolved after excluding an outlier study in children receiving asparaginase[20] and was also related to recent studies that specifically included patients at high risk of VTE. The inclusion of screening-detected or incidental VTE in the primary outcome could be a further determinant of heterogeneity. It

should be considered that it has not been determined whether these events have different prognoses.[50] Our analysis cannot answer the issue of the duration of anticoagulant prophylaxis in cancer patients receiving chemotherapy. Thanks to new anticancer treatments, the life expectancy of patients with several types of cancer has increased dramatically. The duration of prophylaxis tested in the studies included in this meta-analysis ranged from a minimum of 4 weeks to a maximum of 6 months for studies having VTE as the primary outcome and to a maximum of 12 months in studies having death as the primary outcome. Whether longer-lasting prophylaxis could be of benefit and maintain the same safety profile remains undefined. Finally, further data are required on the efficacy and safety of anticoagulant prophylaxis in patients receiving newer anticancer therapies, such as immunotherapy or biologics.

Our study also has some strengths. This is a meta-analysis of randomized studies, with results consistent across different sensitivity analyses and no heterogeneity. Moreover, differently from previous meta-analyses, we limited our primary efficacy analysis to randomized clinical trials with VTE as the primary outcome. Even though high-quality trials with death as the primary outcome have been conducted in this setting, our choice was aimed at reducing heterogeneity related to the use of therapeutic regimens of anticoagulants, to the longer duration of anticoagulant treatment and to gaining a more

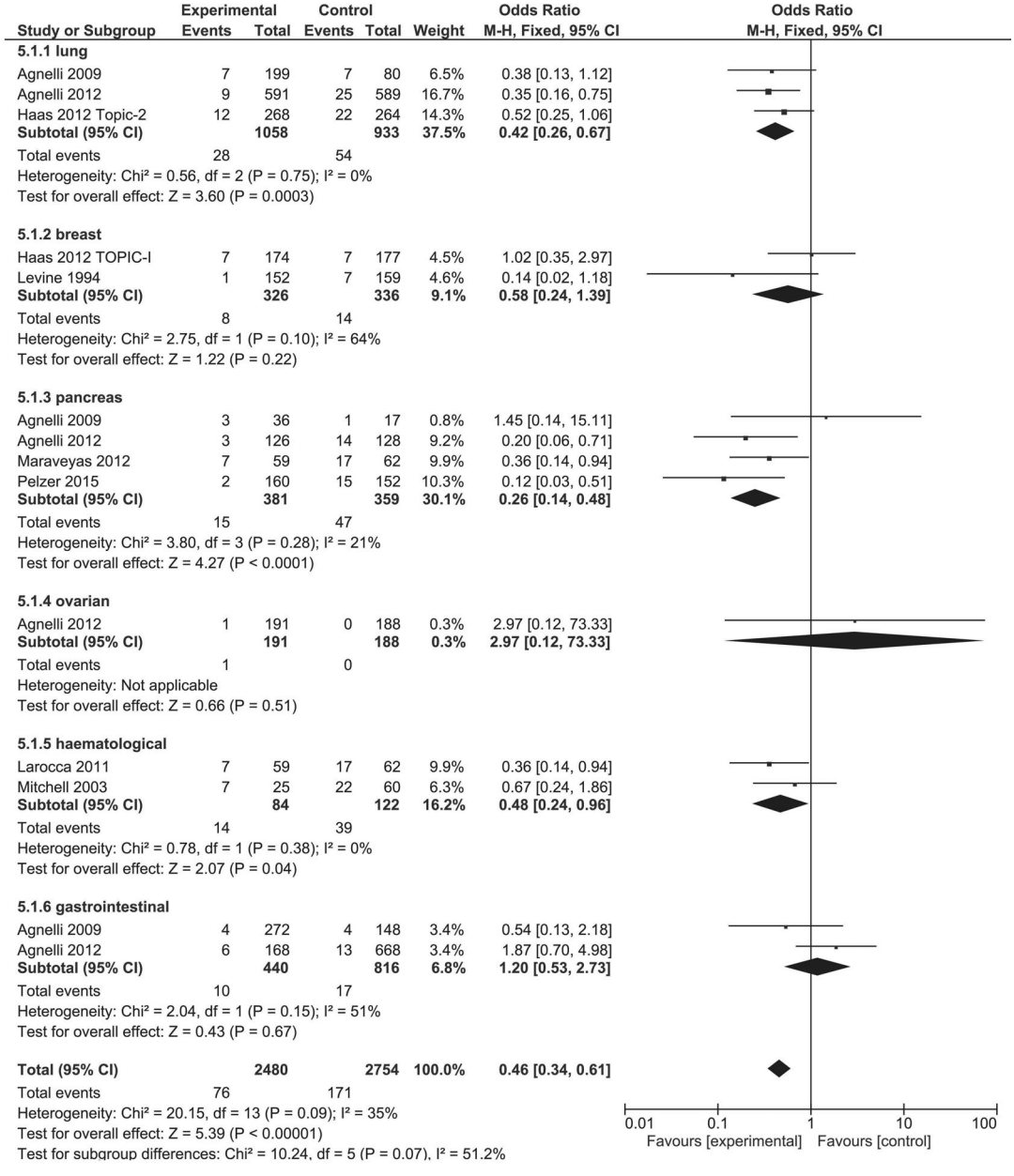

Figure 3. Efficacy of anticoagulant prophylaxis for the prevention of venous thromboembolism in ambulatory cancer patients receiving chemotherapy according to the primary site of cancer.

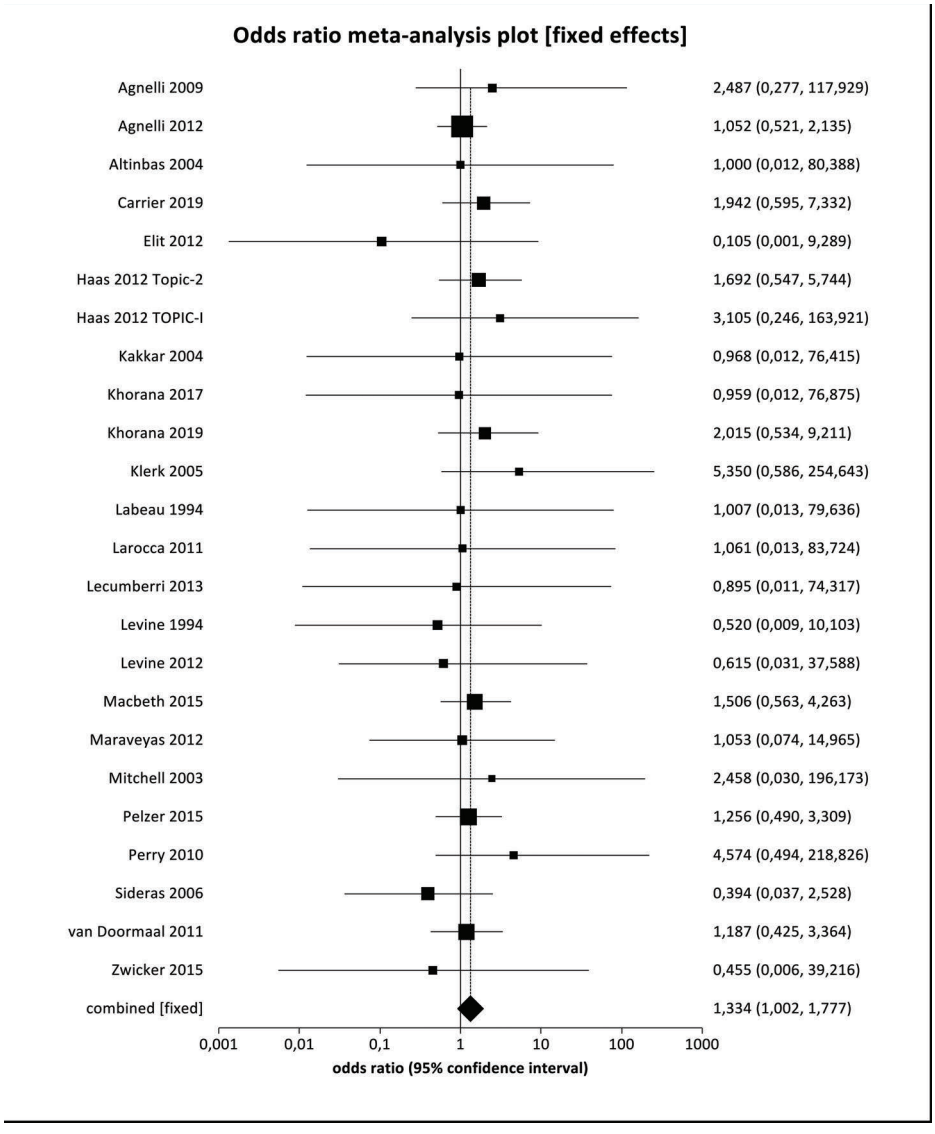

Figure 4. Effect of anticoagulant prophylaxis on the incidence of major bleeding in ambulatory cancer patients receiving chemotherapy.

accurate assessment of the incidence of VTE during follow-up. However, the pooled analysis of all the trials with VTE or death as the primary outcome confirmed the efficacy of anticoagulants without heterogeneity. Moreover, to remain on the safe side, the primary safety analysis of major bleeding in our study included all the trials and did not show any safety signal.

In conclusion, we found that anticoagulant prophylaxis is effective and acceptably safe in ambulatory cancer patients treated with chemotherapy. The selection of the most suitable candidates (patients at increased risk of VTE) for anticoagulant prophylaxis among ambulatory cancer patients treated with chemotherapy is a crucial issue and further studies are required to optimize the efficacy of this intervention.

Acknowledgments

We are indebted to Martina Savoia from the University of Perugia for her assistance in the literature search and preparation for data analysis.

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