SUPPLEMENTARY APPENDIX

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

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Supplemental data

Methods

Search strategy

We performed an unrestricted search in MEDLINE and Scopus through December 2018. Search criteria included the terms “cancer AND venous thromboembolism AND prevention” and “cancer AND venous thromboembolism AND prophylaxis”. No language restrictions were applied. Reference lists of retrieved articles and review articles were manually searched to implement our search. Only full articles were considered for analysis.

One author (C.B.) performed the electronic search and listed the trials that were eligible for inclusion in the study. Study selection was independently performed by two authors (C.B. and M.V.) using predetermined criteria. Two authors (C.B. and M.V.) independently reviewed each study for quality assessment and extracted data on studies and patient characteristics, as well as outcomes, using standardized extraction forms. Disagreements were resolved through revision by an additional reviewer (G.A.) and by discussion.

The following inclusion criteria were considered a) studies not on post-operative VTE prevention; b) studies including at least one comparator arm not receiving anticoagulant prophylaxis; c) objective confirmation of non-fatal VTE.

For duplicate publications, the most recent study was considered.

Studies were included in the meta-analysis if the following data were available: numbers of patients with/without study outcome in patients randomized to anticoagulant/comparator.

Data extraction

For each study, the following data were extracted independently by two authors: general data (study design, year of publication), patients (number, mean age, gender, site of cancer, number at estimated high risk for VTE), anticoagulant prophylaxis (agent, regimen, duration), study procedures

(randomization process, treatment allocation, blinding process), follow up (duration, screening for VTE, patients lost to follow-up) and clinical outcomes (VTE, major bleeding, symptomatic VTE, fatal VTE).

Supplemental Table 1. Additional inclusion and exclusion criteria of selected studies

Author, year	Inclusion criteria	Exclusion criteria
evine, 1994	metastatic breast carcinoma had been receiving first-line or second-line chemotherapy for 4 weeks or less.	ECOG ≥3, underlying bleeding disorder or active peptic ulcer disease, direct bilirubin >2 normal, INR ≥1, platelet count < 50 x 109/L, a history of alcohol abuse, overt brain metastases, presence of an underlying psychiatric or affective disorder, requirement for long-term oral anticoagulant therapy, expected survival < 3 months, concurrent hormonal therapy, and inability to attend follow-up visits
Mitchell, 2003	newly diagnosed ALL age > 6 months and <18 years, at the beginning of the induction chemotherapy (which included ASP), a functioning central venous line (CVL) placed < 2 weeks of initiating induction chemotherapy; informed consent	previous treatment with ASP, known hypersensitivity to any of the ingredients in antithrombin concentrate, medical conditions that could have interfered with participation or assessment of the study drug, received other investigational drugs within 30 days of enrolment, or required treatment with therapeutic anticoagulation.
Agnelli, 2009	metastatic or locally advanced lung, gastrointestinal pancreatic, breast, ovarian, or head and neck cancer Ambulatory patients > 18 years of age receiving chemotherapy for	Patients on adjuvant chemotherapy, venous or arterial thromboembolism < 3 months; antithrombotic treatment for any indication; life expectancy < 3 months; ECOG > 2; active bleeding or bleeding requiring hospitalisation or transfusion or surgical intervention < 4 weeks; intracranial bleeding < 6 months; high risk of bleeding; known active gastric or duodenal ulcer; known cerebral metastasis; severe and uncontrolled hypertension
Perry, 2010	newly diagnosed, pathologically confirmed WHO Grade 3 or Grade 4 glioma Over 18 years of age.	Acute or chronic DVT demonstrated objectively, evidence of serious hemorrhage < 4 weeks, INR> 1.5, platelet count < 100 · 109 per L, symptomatic intracranial or intratumoral bleeding, acute peptic ulcer disease, familial bleeding diathesis, requirement for long-term anticoagulants, uncontrolled hypertension, significant renal failure prior history of documented VTE, an allergy to anticoagulants, an expected lifespan of < 6 months and

		body weight < 40 kg; if they were: pregnant, of childbearing potential and not using adequate contraception, geographically inaccessible for follow-up, or unable to commence study drug within 4 weeks of original surgery or biopsy.
Larocca, 2011	Newly diagnosed multiple mieloma,Previously untreated patients; age between 18 and 65 years, enrolled in the phase 3 trial were assessed for eligibility to be enrolled in the substudy.	history of DVT or arterial thromboembolic events within the past 12 months; clear indication or contraindication for antiplatelet or anticoagulant therapy; active bleeding; high risk of bleeding.
Haas, 2012	objectively proven, disseminated metastatic breast carcinoma TOPIC-1: Adult patients , receiving first- or second-line chemotherapy.	inflammatory breast cancer; receiving anthracycline monotherapy or gemcitabine (monotherapy or in combination); bedridden; previous VTE; current heparin or oral anticoagulant therapy; long-term aspirin or other current antiplatelet drugs; active gastrointestinal bleeding; hemorrhagic stroke; hereditary bleeding disorder; thrombocytopenia partial thromboplastin time >2 times upper limit of normal (ULN); known hypersensitivity to heparin; severe diabetic retinopathy; creatinine >2 times ULN; osteoporotic fracture; myocardial infarction in the preceding 6 months; and participation in a clinical trial with an experimental drug in the preceding 4 weeks.
Haas, 2012	objectively proven, inoperable disseminated primary non–small cell lung carcinoma of stage III or IV TOPIC-2: Adult patients with receiving standard first- or second-line chemotherapy.	if they had small-cell lung carcinoma, brain metastases, hemoptysis of grade 2, or a Karnofsky index <70, bedridden; previous VTE diagnosis; current heparin or oral anticoagulant therapy; long-term aspirin or other current antiplatelet drugs; active gastrointestinal bleeding; hemorrhagic stroke; hereditary bleeding disorder; thrombocytopenia partial thromboplastin time >2 times upper limit of normal (ULN); known hypersensitivity to heparin; severe diabetic retinopathy; creatinine >2 times ULN; osteoporotic fracture; myocardial infarction in the preceding 6 months; and participation in a clinical trial with an experimental drug in the preceding 4 weeks.
Agnelli, 2012	metastatic or locally advanced cancer of the lung, pancreas, stomach, colon or rectum, bladder, or ovary.	life expectancy of less than 3 months, ECOG performance status of 3 or higher, calculated creatinine clearance of less than 30 ml per minute, major surgery within 4 weeks before

	18 years of age or older and planned to receive a course of chemotherapy	randomization, and any contraindication to anticoagulation or requirement for thromboprophylaxis.
Maraveyas, 2012	histopathological or cytological diagnosis of non-resectable, recurrent or metastatic pancreatic adenocarcinoma no obvious thromboembolism; Karnofsky performance status of 60–100; age >18 years, estimated life expectancy >12 weeks, measurable or evaluable disease in baseline CT of thorax/abdomen/pelvis, no incidental imaging evidence of VTE at entry, adequate haematological function creatinine clearance >50 ml/min, INR <1.5, no obvious contraindication to anticoagulation and bilirubin <1.5 · upper limit of normal – with or without biliary stent.	previous gemcitabine-containing treatment; comorbidities which would compromise informed consent or compliance; other advanced malignancy; ongoing anticoagulation treatment and treatment with antiplatelet agents (e.g. aspirin at dose >75 mg, clopidogrel etc.); thromboembolic event in the 6 months before randomisation; Central venous access devices and inferior vena cava filters
Levine, 2012	advanced or metastatic lung, breast, GI (colon, rectum, pancreas, stomach), bladder, cancer of unknown origin, ovarian or prostate cancer, myeloma or selected lymphomas, over 18 years of age; receiving either first-line or second-line chemotherapy; able to begin study medication within 6 weeks of starting either first-line or second-line chemotherapy; expected course of chemotherapy was $\geq$ 90 days	women of childbearing potential who were unwilling or unable to use an acceptable method of contraception to avoid pregnancy for the entire study period, who were using a prohibited contraceptive method, or who were pregnant or breastfeeding; prior history of documented DVT or PE; active bleeding or high risk for bleeding; having a serious hemorrhage that had required hospitalization, transfusion or surgical intervention < 4 weeks; familial bleeding diathesis; overt metastasis of cancer to the brain; expected survival < 6 months or an ECOG > 3; candidate for bone marrow transplantation < 12-week treatment period or 30-day follow-up period; uncontrolled hypertension; INR > 1.5, or platelet count < 100 · 109 L) if not yet receiving chemotherapy, or platelet count < 50 · 109 L)1 if receiving chemotherapy; alanine aminotransferase >3 times the ULN; total bilirubin >2 times the ULN; calculated creatinine clearance of < 30 mL min)1; and requiring long-term oral anticoagulant therapy, > 165 mg daily aspirin, clopidogrel, cilostazol, or aspirin–dipyridamole.
Pelzer, 2015	outpatients with histologically confirmed APC, no previous radiotherapy or chemotherapy, KPS 60%, measurable tumor lesion confirmed by computed tomography or magnetic resonance imaging within the last 14 days, no VTEs within the last 2 years, sufficient bonemarrowfunction (leukocytes 3.5 109/L; thrombocytes 100 109/L), age 18 years, adequate compliance, and residence within geographic	preexisting anticoagulation indication, major hemorrhage < 2 weeks or severely impaired coagulation, active GIulcers, major surgery < 2 weeks, body weight 45 kg or 100 kg, pregnant, lactating or insufficient contraception during study, severe concomitant disease incompatible with study participation (eg, psychiatric), hypersensitivity to one of the drugs used or to structurally similar drugs, and severely impaired renal function (creatinine clearance 30 mL per minute).

	proximity to the particular department (allowing adequate follow-up).	
Zwicker, 2015	adenocarcinoma of the pancreas (locally advanced or metastatic), colorectal (stage IV), non-small cell lung cancer (stage III or IV), relapsed or stage IV ovarian, or surgically unresectable or metastatic gastric adenocarcinoma histologically confirmed malignancy for which standard curative therapies do not exist. < 4 weeks of first or second line therapy for the malignancy, a life expectancy estimated to be >6 months, and an ECOG ≤ 2. absolute neutrophil count ≥ 1.0 × 109 platelet count ≥ 100 × 109/l, aspartate transaminase or alanine transaminase ≤3.0-fold ULN, creatinine clearance ≥ 40 ml/min.	Known brain metastases, history of VTE <5 years, or any history of significant haemorrhage requiring transfusion or hospitalization < 5 years (outside of a surgical setting). history of allergy to heparin compounds, history of heparin-induced thrombocytopenia, prothrombin time or partial thromboplastin time >1.2-fold UNL, a familial bleeding diathesis, disseminated intravascular coagulation, or requirement for anticoagulation or an antiplatelet agent (>81 mg aspirin daily).
Khorana, 2017	Patients had to have a histologic diagnosis ofmalignancy, be at the planned initiation of a new systemic chemotherapy regimen (either initial or after progression on prior chemotherapy), be 18 years of age or older and provide written, informed consent. Patients had to be at high-risk for developing VTE, based on a risk score of ≥3	active bleeding or high risk for bleeding; primary brain tumor,myeloma, leukemia or myelodysplastic syndrome; planned stemcell transplant; life expectancy <6 months; known allergy to heparin or LMWH; patient or caregiver incapable of self-injection; acute or chronic renal insufficiency with creatinine clearance <30 mL/min; history of heparin induced thrombocytopenia; allergy to intravenous contrast; pregnancy; need for anticoagulant therapy; or, platelet count <75,000/mm3.
Khorana, 2019*	18 years of age or older, ambulatory (outpatients) with a solid tumor or lymphoma, baseline Khorana score of 2 or higher, and an expected survival of greater than 6 months with a plan to start a new systemic regimen within 1 week of initiating study drug	primary brain tumors or known brain metastases, ECOG≥, active bleeding, or at risk for bleeding
Carrier, 2019	newly diagnosed cancer or progression of known cancer after complete or partial remission and who were initiating a new course of chemotherapy with a minimum treatment intent of 3 months. Inclusion required a Khorana score of 2 or higher, an	increased risk for clinically significant bleeding; hepatic disease associated with coagulopathy; a cancer diagnosis consisting solely of basal-cell or squamous-cell skin carcinoma, acute leukemia,or myeloproliferative neoplasm; a planned stemcell transplantation; a life expectancy <6 months; renal insufficiency GFR < 30 ml per minute per 1.73 m2 of body-surface area; or a platelet count < 50,000 per cubic millimeter. the use

	age of 18 years or older, and the capacity to provide written informed consent.	of medications contraindicated with apixaban, pregnancy or potential pregnancy, breast-feeding, the use of continuous anticoagulation, and a weight of less than 40 kg.

* 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

Supplemental Table 2a. Study quality assessment

Author, Year	randomization	appropriate method of random	blinding	appropriate blinding	appropriate long term FU
Studies with VTE as primary outcome					
Levine, 1994[19]	1	1	1	1	1
Mitchell, 2003[20]	1	1	0	open	
Agnelli, 2009[21]	1	1	1	1	1
Perry, 2010[22]	1	1	1	1	1
Larocca, 2011[23]	1	1	0	open	
Haas, 2012[24]	1	1	1	1	1
Haas, 2012[24]	1	1	1	1	1
Agnelli, 2012[25]	1	1	1	1	1
Maraveyas, 2012[26]	1	1	0	open	
Levine, 2012[10]	1	1	1	1	1
Pelzer, 2015[27]	1	1	0	open	
Zwicker, 2015[28]	1	na	0	open	
Khorana, 2017[29]	1	1	0	open	
Khorana, 2019[!1]	1	1	1	1	1
Carrier, 2019[12]	1	1	1	1	1
Studies with death as primary outcome					
Labeau, 1995[30]	1	1	0	open	1 lost
Kakkar, 2004[31]	1	1	1	1	1
Altinbas, 2004[32]	1	1	0	open	5 lost
Klerk, 2005[33]	1	1	1	1	1
Sideras, 2006[34]	1	1	partially	partially	na§
van Doormaal, 2011[35]	1	1	0	open	46 patients lost/widrawn consent
Elit, 2012[36]	1	1	0	open	1*
Lecumberri, 2013[37]	1	1	0	open	1 patient lost°
Macbeth, 2015[38]	1	1	0	open	1#

§ Stopped after first interim analysis

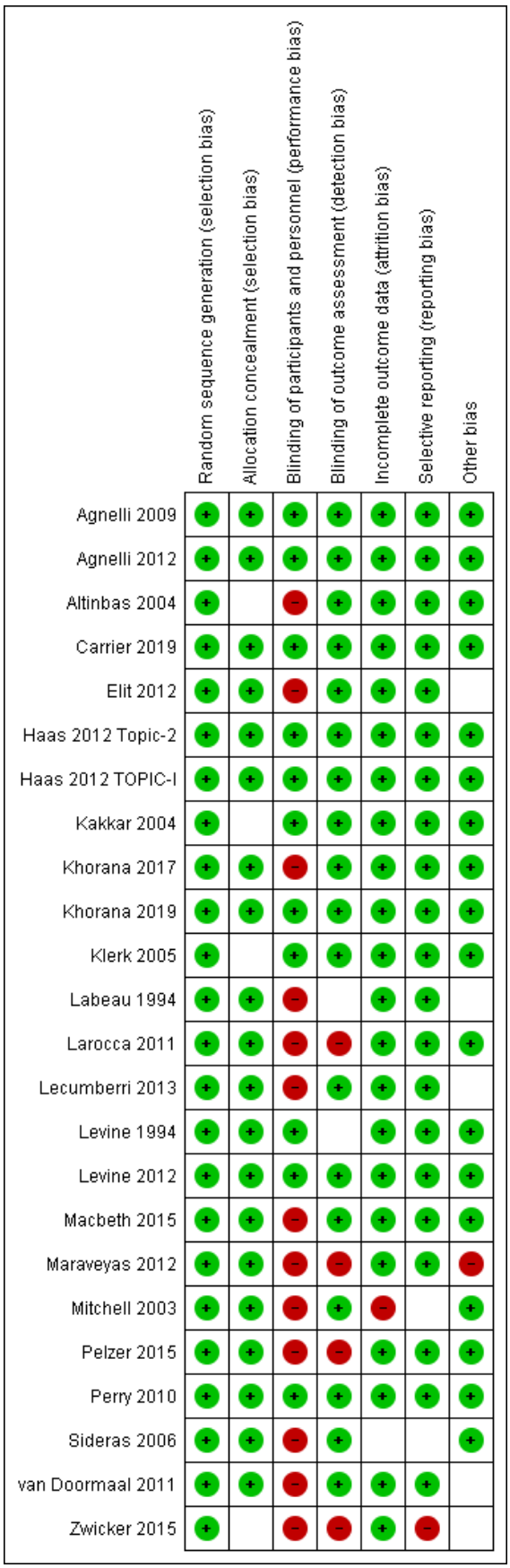
*Premature interruption slow recruitment

° Premature interruption slow recruitment

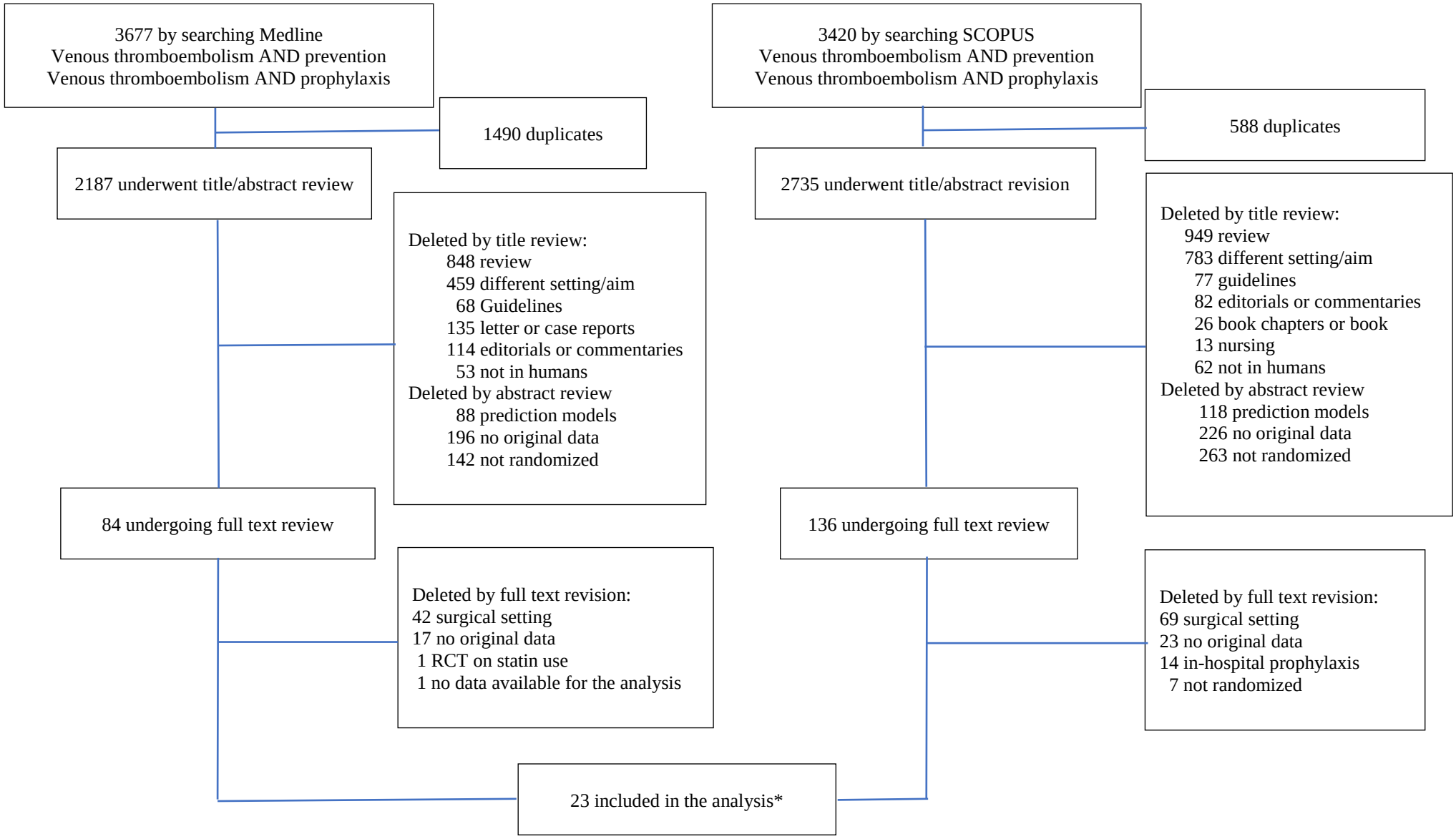
Did not reach the intended number of outcome events

Na= not available

Supplemental Table 2b. Study quality assessment according to the Cochrane risk assessment tool

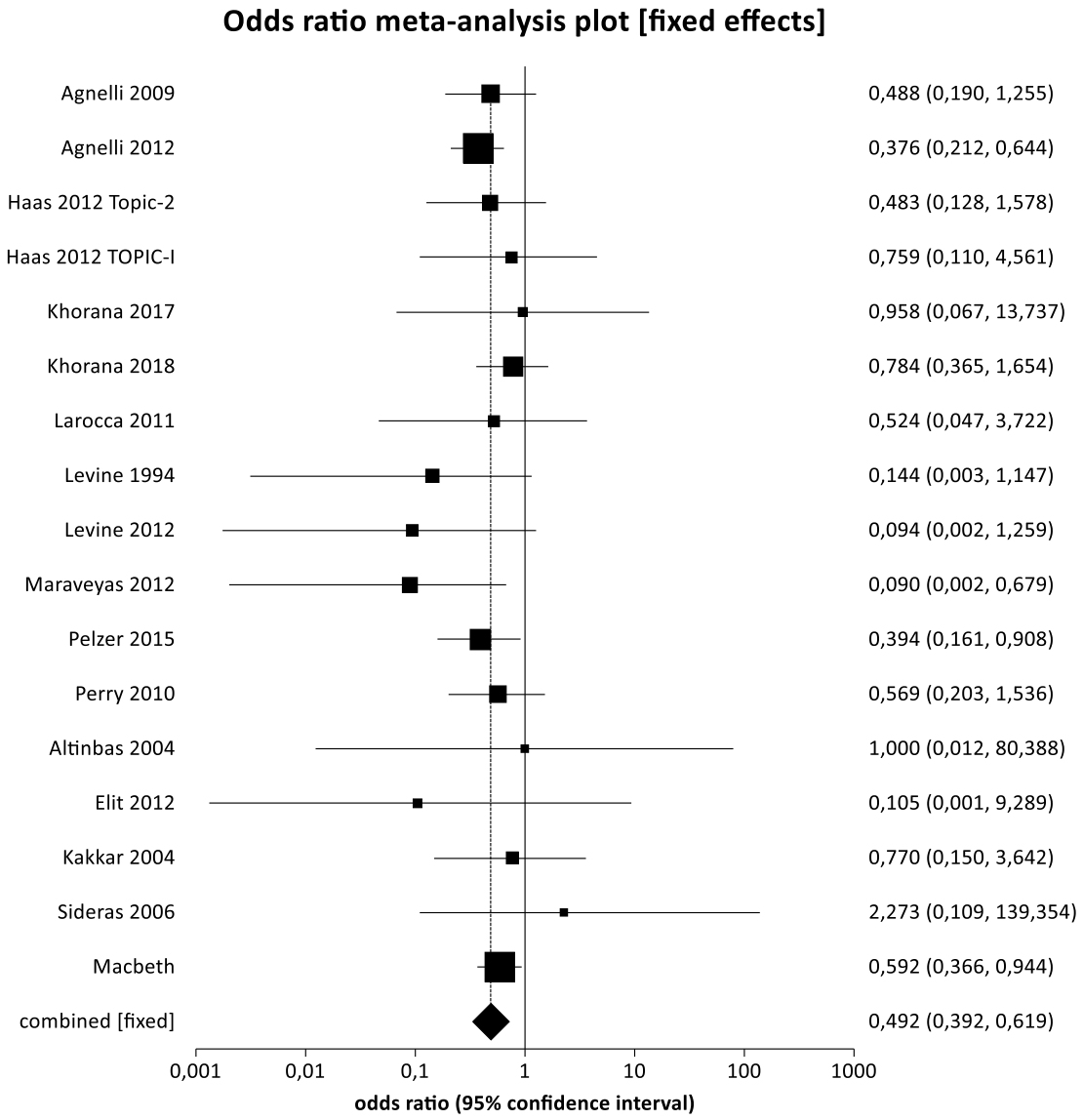


Supplemental Figure 1. Flow diagram for study selection



*one paper reported on two individual randomized studies

Supplemental Figure 2 Symptomatic VTE in studies with VTE or death as primary outcome



I_2 (inconsistency) = 0% (95% CI = 0% to 44,5%)