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Systematic review and meta-analysis of the risk of severe and life-threatening thromboembolism in cancer patients receiving anti-EGFR monoclonal antibodies (cetuximab or panitumumab)

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Cancer-associated thromboembolism is a substantial problem in clinical practice. An increase in the level of fibrinopeptide A (a substance associated with hypercoagulable states) has been observed in humans exposed to fluorouracil. Anti-EGFR monoclonal antibodies cetuximab and panitumumab, which are now widely used in patients with metastatic colorectal cancer, could prolong the uncovering of endothelial structures resulting from flouorouracil or other co-administered agents, thus favouring several factors leading to thromboembolism. We performed a systematic review and meta-analysis of randomised, controlled trials assessing whether cancer patients receiving anti-EGFR monoclonal antibodies cetuximab and panitumumab are at increased risk of thromboembolic events. We searched electronic databases (Medline, Embase, Web of Science, Central) and reference lists. Phase II/III randomised, controlled trials comparing standard anti-cancer regimens with or without anti-EGFR monoclonal antibodies and reporting serious venous thromboembolic events were included in the analysis. Seventeen studies (12,870 patients) were considered for quantitative analysis. The relative risk (RR) for venous thromboembolism (18 comparisons) was 1.46 (95% CI 1.26 to 1.69); the RR of pulmonary embolism, on the basis of eight studies providing nine comparisons, was 1.55 (1.20 to 2.00). Cancer patients receiving anti-EGFR monoclonal antibodies-containing regimens are approximately 1.5 times more likely to experience venous or pulmonary embolism, compared to those treated with the same regimens without anti-EGFR monoclonal antibodies. Clinicians should consider patient's baseline thromboembolic risk when selecting regimens that include cetuximab or panitumumab. Potential non-reporting of these important adverse events remains a concern. PROSPERO registration number is CRD42014009165.

Introduction

Cancer patients have an acquired thrombophilic condition predisposing them to thromboembolic events, which increase morbidity, mortality and economic burden.[1,2] The relationship between malignancy and thromboembolism has been demonstrated in many epidemiological studies with venous thrombosis occurring in 4–20% of patients with cancer.[3] The annual incidence ranges from 0.5% to over 1%, compared to 0.1% in the general population.[4] Overall, cancer patients constitute 15–20% of the patients diagnosed with venous thromboembolism.[5] Venous thromboembolic events (VTE) and thrombotic complications have been listed as the second most frequent cause of death in patients with cancer[5,6,] with 1-year survival of cancer patients diagnosed with VTE reported as one third that of cancer patients without VTE (matched for age, sex, type, and duration of the malignancy) in a registry study.[4]

Thromboembolic events may present as a range of conditions including deep vein thrombosis (DVT), pulmonary embolism (PE), nonbacterial thrombotic endocarditis, superficial thrombophlebitis, catheter-related thrombosis, hepatic veno-occlusive disease, and also arterial thrombosis, each of which frequently require long-term anticoagulation therapies and interruption of chemotherapy.[6–8]

The hypercoagulable state in cancer involves various complex interdependent mechanisms, including interaction among cancer cells, host cells, and the coagulation system. Cancer patients are also subject to non-oncologic risk factors

Key words: anti-EGFR, cancer, thromboembolism, meta-analysis, safety, adverse events, pharmacovigilance, systematic review, cetuximab, panitumumab
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What's new?

While monoclonal antibodies (MoAbs) targeting the epidermal growth factor receptor (EGFR) are effective anticancer agents, their use is associated with an increased risk of severe thromboembolism, a condition to which some cancer patients are predisposed. Nonetheless, the degree to which anti-EGFR MoAbs contribute to this risk was unclear. In this systematic review of 17 different studies, thromboembolic events were found to be 1.5 times more likely in cancer patients treated with anti-EGFR MoAb-containing regimens than in patients given the same regimens but without MoAbs. Relative risk of thromboembolic events did not vary significantly between cancer types.

of thromboembolism including: surgical interventions, immobilization, infections, and, in particular, drug exposure may greatly amplify the overall risk at various time points.[9] Several systematic reviews have explored the magnitude of this risk associated with various anti-cancer agents such as cisplatin, thalidomide, or novel therapies such as anti-angiogenic agents targeting vascular endothelial growth factor receptor (EGFR). However, to date, the knowledge on the potential impact of many anti-cancer drugs on thromboembolism is limited.[5]

Cetuximab and Panitumumab, a chimeric and a fully human monoclonal antibody, respectively, are two anti-EGFR agents with demonstrated efficacy as anti-cancer agents[10,11] which are now incorporated routinely into several therapeutic regimens. These monoclonal antibodies (MoAbs) bind to the epidermal growth factor receptor (EGFR), a member of the ErbB family which is constitutively expressed in many normal epithelial tissues and expressed at high levels in about one third of epithelial cancers. Its activation appears to be critical for the growth of many tumors.[12] Anti-EGFR MoAbs, block interaction of EGF with its specific receptor in both tumour and normal cells, inhibiting receptor phosphorylation. This results in down-regulation of EGF receptors and modulation of pivotal processes impacting on tumour growth and progression such as angiogenesis, induction of apoptosis, tumour invasiveness and metastatic spread.[13,14] For these reasons, EGFR is considered as a prominent therapeutic target for MoAbs-based immunotherapy in cancer.[15,16]

The anti-EGFR antibodies cetuximab and panitumumab are effective in different lines of treatment and in several combinations in the management of neoplasia such as colorectal cancer. Although beneficial, these agents have been associated with increased incidence of severe harms including skin rash, electrolyte abnormalities, especially magnesium-wasting syndrome, haematological disorders, infusion reactions and thromboembolic events.[17,18]

To the best of our knowledge, the only systematic review examining the risk of thromboembolism was published in 2012.[19] In this analysis events occurring in patients treated with anti-EGFR antibodies and EGFR-Tyrosine kinase inhibitors were combined. Anti-EGFR antibodies and EGFR-Tyrosine kinase inhibitors belong to two distinct classes of anti-EGFR drugs with different pharmacokinetic and pharmacodynamic properties and, conceivably different safety profiles[20], thus it appears more appropriate to analyse them separately.

As the indications for use of anti-EGFR monoclonal antibodies are increasing, we carried out an updated and comprehensive systematic review that focuses specifically on cetuximab and panitumumab to better define their patterns of vascular toxicity in cancer patients. We also explored potential differences in the relationships between different cancers and type of MoAbs with the aim of providing clinicians with solid evidence on which to plan therapies and optimize risk management strategies.

Methods

Aims and objective

To assess the potential risk of developing severe thromboembolic AEs in cancer patients treated with cetuximab or panitumumab combined with standard therapeutic regimens.

Protocol registration

As recommended by the PRISMA statement and more recently PRISMA-P[21,22] all planned review methods were specified in a protocol which was registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO: CRD42014009165).

Information sources and searching

Medline, Embase, Central, Web of Science and the WHO platform for Clinical Trials were searched from inception until 1st October 2014. The base search strategy was constructed using Medline and then adapted to the other resources searched. We also carried out a manual search of the bibliographies of relevant studies. A complete literature search strategy is reported in Supporting Information Appendix (Online extra). An update of literature search was performed in April 2016 to implement most recently released data in our analyses.

Inclusion criteria

Prospective phase II or III randomised controlled trials comparing a standard regimen plus anti-EGFR monoclonal antibody with the same standard regimen alone in cancer patients were eligible for inclusion. Studies written in English and reporting data on the number of thromboembolic adverse events (AEs) were considered. Phase I trials, single-arm phase II or III trials, trials comparing different backbone regimens with anti-EGFR MoAbs were excluded (Fig. 1). F1

Data collection

Data were extracted independently by two investigators (MM and CS) with discrepancies resolved by consulting a third reviewer

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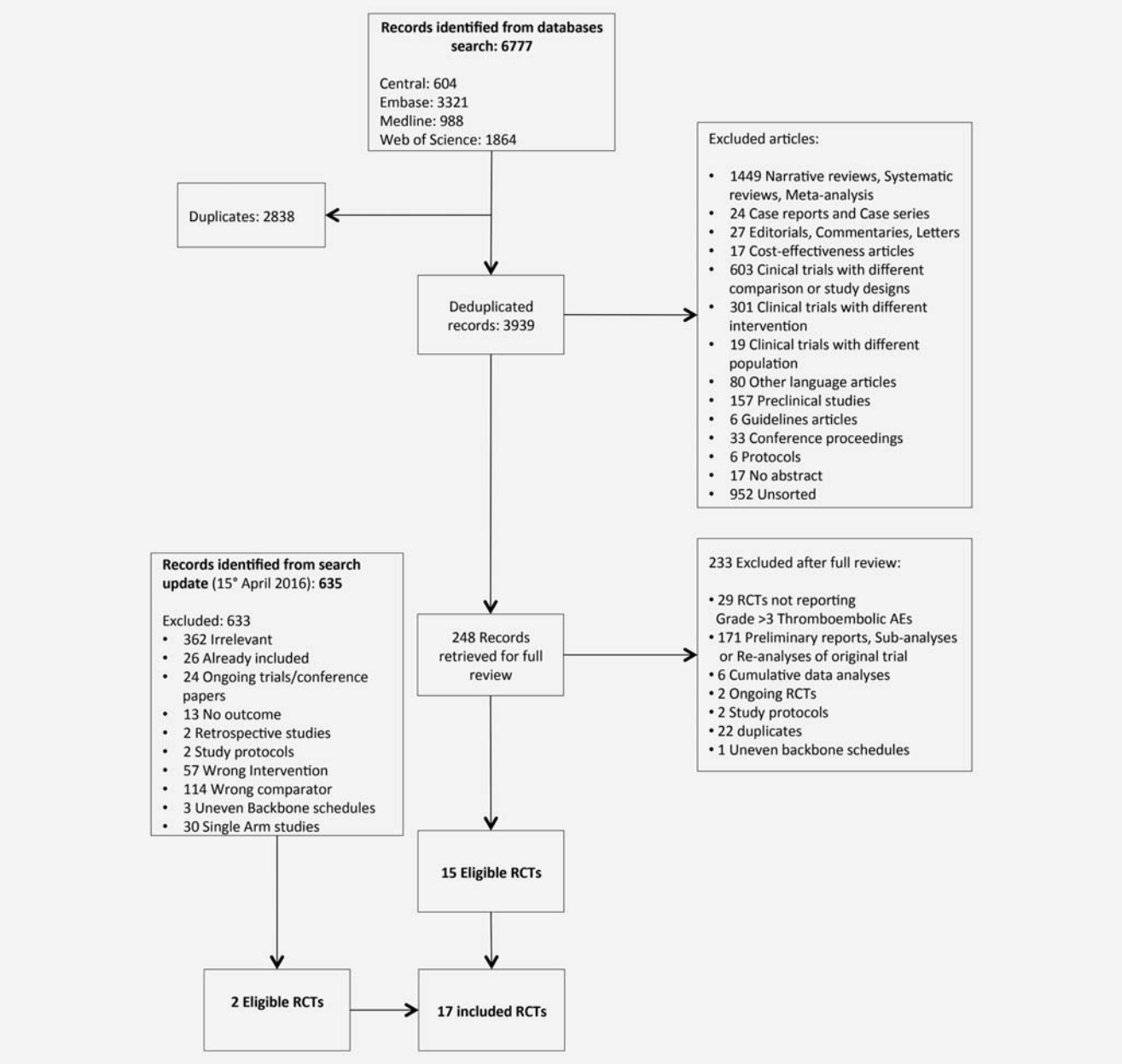

Figure 1. Flow diagram of the study selection process for the systematic review.

(GC). Multiple papers reporting the results of the same cohort were handled by considering only the one reporting the largest population. For each study, we extracted year of publication, trial phase, treatment delivered on each arm, planned anti-EGFR MoAbs doses, underlying malignancy, number of participants enrolled, number of participants evaluable for safety analysis, median age, median follow-up duration and type of thromboembolic events of interest, including the number of VTEs and their severity.

AEs were as reported by each trial, and defined by criteria established by the WHO, Cancer and Leukemia Group B, or National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 2 or 3.[23,24] All reported grade 3–4 thromboembolic AEs in each arm of treatment were recorded and classified as deep venous thrombosis (DVT), pulmonary embolism (PE), or unspecified thromboembolism. As we planned to conduct a specific analysis for PE, where study publications reported only a combined thromboembolic AEs category, we contacted authors to seek clarification of the number and type of thromboembolic events that had occurred.

Risk of bias assessment

Two authors (MM and CS) independently evaluated risk of bias using Cochrane Risk of Bias tool.[25] This was modified by removing the item on selective outcome reporting, as

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reporting of the adverse events under investigation was an inclusion criteria. Also, clinical studies having as primary outcome effectiveness and not drug safety do not generally provide sufficient information to establish if selective reporting related to a specific AE occurred.

Statistical Analysis

We calculated the risk of Grade 3–4 VTE AEs by dividing the number of patients experiencing DVT, PE or unspecified thromboembolism AEs in each arm by the total number of patients evaluated for toxicity. If the latter was not presented, the total of patients enrolled in each arm was used as denominator. The ratio of these risks was used to calculate relative risk (RR) and the 95% confidence interval for each AE considered. Computed values for each study were then combined in meta-analyses using both fixed-effects and random-effects models.[26] As very few thrombotic events were anticipated, we used the Mantel-Haeszel method[27] and logistic regression modelling.[28] For each meta-analysis, the Cochran Q test and the I-squared statistic were calculated to estimate between-trial heterogeneity.

We conducted sensitivity analyses to explore the influence of the following factors on the size of the effect and on heterogeneity: co-administration of anti-angiogenic drugs (excluding trials with bevacizumab-containing regimens), treatment exposure (excluding trials with difference in drug exposure between arms) and need of palliative treatment (excluding trials on patients with advanced cancer requiring best supportive care).

Analysis of subgroups

Where data were available, pre-specified subgroup analyses were performed to identify whether treatment effect was modified by risk factors for severe thromboembolism. These included: underlying malignancy; antibody administered (cetuximab or panitumumab) and anti-EGFR scheduled dose.

The overall effect estimate for each outcome was re-expressed as Number Needed to Harm (NNH) across a range of assumed control risks (ACRs) based on event rates in the control arm of all studies.[29] We calculated weighted mean incidence with 95% CI of AEs using rates of the events observed in experimental and control arms of the considered studies. Statistical analyses were carried out using appropriate software, including R, Review Manager, Microsoft Excel.

Results

Study identification and selection

Searches returned 6,777 records. Following de-duplication, titles and abstract of 3,939 records were, screening resulting in 248 potentially eligible studies. These underwent a full text evaluation resulting in 15 randomised clinical trials (RCTs) that fulfilled all inclusion criteria (Fig. 1).[30–45] The literature search update performed in April 2016 returned 635 additional records, that, after a literature selection process, provided two clinical trials meeting inclusion criteria. We contacted authors of nine relevant studies asking for further data on thromboembolism (Supporting Information Appendix). Four authors replied, unfortunately none could provide the data requested.

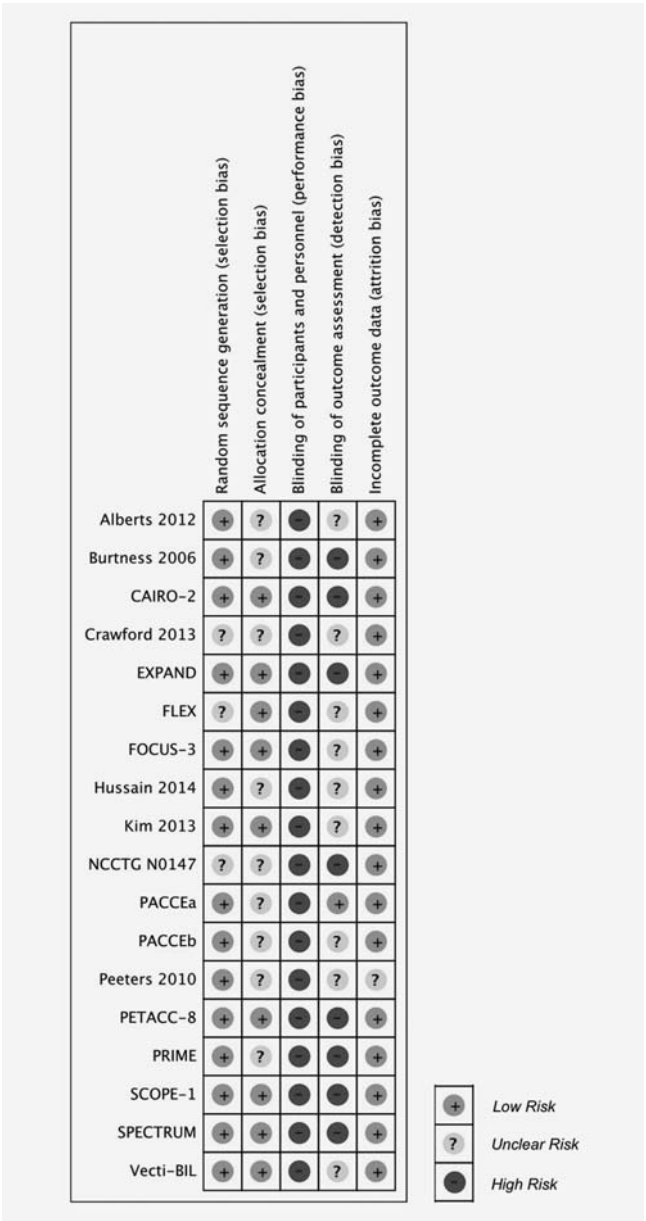

Figure 2. Risk of bias of included RCTs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Study, patients, and treatment characteristics

Overall, 17 studies, carrying out 18 comparisons, were included in the analyses. Of these, 11 reported data on cetuximab[30–37,41,43] and 6 on panitumumab[38–40,42,44,45] (Table 1). T1
Taken together, all the included RCTs reported data on a total population of 12,870 patients suffering from: colorectal cancer (8 studies,[30,32,37,39–42] 8,931 patients), non-small cell lung cancer (3 studies,[34,36,38] 1,857 patients), gastro-oesophageal cancer (2 studies,[34,44] 1,140 patients), squamous cell head and neck

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Table 1. Summary characteristics of the included studies

Study ID	Trial phase	Underlying malignancy	Number of randomized		Safety population		Treatment arm A	Treatment arm B	Anti-EGFR scheduled dose[1]	Median duration of follow-up	Time-point of AEs assemment
			arm a	arm b	arm a	arm b					
Alberts 2012[30]	3	mCRC	909	954	894	931	mFOLFOX6 + Cet	mFOLFOX6	Cet400mg/m^2; Cet250mg/m^2	28 months (0-68)	NR
Burtness 2006[31]	3	SCHNC	57	60	58	58	Cisplatin + Cet	Cisplatin	Cet400mg/m^2; Cet250mg/m^2	NR	NR
CAIRO2[32]	3	mCRC	368	368	366	366	Capec+Bev + Cet	Capec+Bev	Cet400mg/m^2; Cet250mg/m^2	NR	NR
Crawford[38]	2	NSCLC	112	54	112	54	Carboplatin + Paclitaxel+ Pan	Carboplatin + Paclitaxel	Pan 6 mg/kg	NR	NR
EXPAND[33]	3	Gastric	445	449	446	436	Capec+Cisplatin + Cet	Capec+Cisplatin	Cet400mg/m^2; Cet250mg/m^2	20.0–24.9 months	30 days ALDR
FLEX[34]	3	NSCLC	557	568	548	562	Cisplatin + Vinorelbine + Cet	Cisplatin + Vinorelbine	Cet400mg/m^2; Cet250mg/m^2	23.8 months (22.1–24.9)	Unclear
FOCUS-3[45]	2	mCRC	47	82	47	82	FOLFIRI + Cet	FOLFIRI	Cet500mg/m^2	NR	Unclear
Hussain 2014[35]	2	Bladder	60	28	59	28	Gemcit + Cisplatin + Cet	Gemcit + Cisplatin	Cet500mg/m^2 onday 1 and 15	17.4 vs 14.3 months	NR
Kim 2013[36]	3	NSCLC	468	470	451	448	Docetaxel or pemetrexed + Cet	Docetaxel or pemetrexed	Cet400mg/m^2; Cet250mg/m^2	NR	NR
NCCTG N01047 (Huang 2014)[37]	3	mCRC	40	106	40	106	FOLFIRI + Cet	FOLFIRI	Cet400mg/m^2; Cet250mg/m^2	5.95 years (0.1-7.0) .	Unclear
PACCEa[39]	3b	mCRC	413	410	407	397	BevOx + Pan (FOLFOX)	BevOx (FOLFOX)	Pan 6 mg/kg	12.3 monthsfor the Ox-CT cohort vs 9.0 for the Iri-CT cohort (0.2 to 26.2)	30 days ALDR
PACCEb[39]	3b	mCRC	115	115	111	113	BevIri + Pan (FOLFIRI)	BevIri (FOLFIRI)	Pan 6 mg/kg	12.3 monthsfor the Ox-CT cohort vs 9.0 for the Iri-CT cohort (0.2 to 18.6)	30 days ALDR
Peeters 2010[40]	3	mCRC	591	595	541	542	FOLFIRI + Pan	FOLFIRI	Pan 6 mg/kg	13.3 vs 10.2 months (0.2-31.7 vs 0.5-32.9)	30 days ALDR
PETACC-8[41]	3	mCRC	1280	1279	1149	1179	FOLFOX4 + Cet	FOLFOX4	Cet1,400mg/m^2; Cet250mg/m^2	3.3 years (3.2–3.4)	30 days ALDR
PRIME[42]	3	mCRC	593	590	539	545	FOLFOX4 + Pan	FOLFOX4	Pan 6 mg/kg	80 weeks (0-201)	30 days ALDR
SCOPE-1[43]	3	Esophageal	129	129	129	129	Cisplatin + Capecitabine + Radiot + Cet	Cisplatin + Capecitabine + Radiot +	Cet400mg/m^2; Cet250mg/m^2	16.8 months (11.2–24.5)	12 weeks AFA

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Table 1. Summary characteristics of the included studies (Continued)

Study ID	Trial phase	Underlying malignancy	Number of randomized		Safety population		Treatment arm A	Treatment arm B	Anti-EGFR scheduled dose[1]	Median duration of follow-up	Time-point of AEs assessment
			arm a	arm b	arm a	arm b					
SPECTRUM[44]	3	SCHNC	327	330	325	325	Cisplatin + FU + Pan	Cisplatin + FU	Pan 9 mg/kg ln 3 weeks	44.0 vs 35.0 weeks (21.0 − 75.0 vs 16.0 − 66.0)	30 day ADLR
Vecti-BIL[45]	2	Biliary tract	45	44	45	44	GemOx + Pan	GemOx	Pan 6 mg/kg	NR	NR

[1]Cetuximab was administered weekly, panitumumab was administered bi-weekly.
ADLR: After Last Dose Received; AFA: After First Administration; Bev: Bevacizumab; BevOx: Bevacizumab Oxaliplatin; Cet: Cetuximab; GemOX: Gemcitabine + Oxaliplatin; FOLFIRI: Leucovorin Fluorouracil Irinotecan; FOLFOX4: Leucovorin Fluorouracil Oxaliplatin; mCRC: metastatic colorectal cancer; mFOLFOX6: Leucovorin Fluorouracil Oxaliplatin; FU: Fluorouracil; NSCLC: Non Small Cell Lung Cancer; NR: Not Reported;; SCHNC: Squamous Cell Head and Neck Carcinoma; Pan: Panitumumab. Notes: "Safety population" consists of the number of patients who received at least one dose of a study drug.

cancer (2 studies,[33,43] 766 patients), bladder cancer (1 study,[35] 87 patients) and biliary tract cancer (1 study,[45] 89 patients). Most used doses were 400 mg/m^2 on day one followed by 250 mg/m^2 weekly for cetuximab and 6.0 mg/kg every 2 weeks for panitumumab. Four studies[35,41,44,45] reported different cetuximab and panitumumab doses (Table 1). As the PACCE trial[39] was a multiple arm study reporting results of two different treatment comparisons, we considered it as two separate double-arm studies (PACCEa and PACCEb).

Risk of bias

Most RCTs adopted appropriate methods to generate random sequences (15[30–33,35,36,38–45] out of 17), but fewer reported appropriate concealment methods (9[32–34,36,38,41,43–45] out of 17). In one study[40] the risk of attrition bias was unclear, but low in all the others. Due to the open label design all the studies are at high risk of performance bias, except for one[41], which was designed as double-blind. However, as reported by the authors, blinding was likely to be compromised by frequent occurrence of Cetuximab-related skin rashes[31]. For the same reason, nine[31–33,37,38,41–44] studies are at high risk of detection bias, and for nine[30,34–36,38–40,45,46] the risk is unclear (Fig. 2). F2

Incidence and RR of venous thromboembolism

Data on grade 3 and 4 thromboembolic AEs were reported in all of the included studies. There were 424 cases of venous thromboembolism out of 6,485 patients in the anti-EGFR MoAbs group and 283 out of 6,514 patients in the control group. The weighted mean incidence observed was 7.8% (95% CI 6.0 to 9.6%) in patients receiving anti-EGFR regimens and 4.6% (95% CI 3.4 to 5.7%) in patients receiving non-anti-EGFR regimens (Table 2). Using the fixed-effect model we found that the anti-EGFR regimens were associated with a higher risk of severe venous thromboembolism compared with the control arm RR was 1.46 (95% CI 1.27 to 1.69) ($I^2$0%, $p = 0.83$) (Table 2, Fig. 3). NNH, calculated using the overall RR, is 56 (95% CI 38 to 100). T2 F3

Incidence and RR of pulmonary embolism

Data on grade 3 and 4 PE events were available for 8 studies (including 9 comparisons as the four-arm PACCE trial was considered as two double-arm studies) including a total population of 7,028 patients. There were 145 cases of PE out of 3,532 patients in the anti-EGFR MoAbs group and 91 out of 3,496 patients in the control group. The weighted mean incidence was 3.8% (95% CI 2.3 to 5.3%) in patients receiving anti-EGFR regimens and 2.7% (95% CI 1.7 to 3.8%) in patients receiving non-anti-EGFR regimens (Table 2). Using the fixed-effect model we found that the anti-EGFR-containing regimens were associated with a higher risk of severe PE compared with the control arm (RR of 1.55; 95% CI 1.20 to 2.00) (I^2 0%, $p = 0.99$) (Table 2). NNH, calculated using the overall RR, is 60 CI (95% CI 33 to 167).

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Table 2. RRs and Mean Weighted Incidences of thromboembolic events

		No of Grade 3–4 AEs/total		Incidence (CI 95%)		
	Number of studies*	Anti-EGFR arm	Control arm	Anti-EGFR arm	Control arm	Relative risk (CI 95%)
Venous Thromboembolism						
Overall	17	424/6,485	283/6,514	7.8% (6.0 to 9.6%)	4.6% (3.4 to 5.7%)	1.46 (1.27 to 1.69)
Cetuximab	10	233/4,360	157/4,414	6.1% (4.5 to 7.6%)	3.7% (2.7 to 4.7%)	1.46 (1.20 to 1.79)
Panitumumab	6	188/2,078	123/2,018	10.7% (6.1 to 15.4%)	6.5% (3.3 to 9.6%)	1.46 (1.18 to 1.80)
Colorectal cancer	7	280/4,424	207/4,507	8.1% (5.3 to 10.8%)	5.5% (3.5 to 7.5%)	1.37 (1.15 to 1.62)
Gastroesophagealcancer	2	41/575	28/565	7.8% (3.3 to 12.3%)	6.0% (0.5 to 11.4%)	1.44 (0.91 to 2.30)
SCHNC	2	27/383	12/383	6.9% (4.3 to 9.4%)	3.1% (1.4 to .4.9%)	2.25 (1.16 to, 4.37)
NSCLC	2	54/952	29/905	6.3% (3.1 to 9.5%)	3.0% (1.6 to 4.4%)	1.61 (1.04 to 2.51)
Bladder cancer	1	17/59	3/28	28.8% (17.3 to 40.4%)	10.7% (0.00 to 22.2%)	2.69 (0.86 to 8.43)
Biliary tract cancer	1	2/45	1/44	4.6% (0 to 10.6%)	2.4% (0 to 6.8%)	1.96 (0.18 to 20.80)
Pulmonary Thromboembolism						
Overall	8	145/3,532	91/3,496	3.8% (2.3 to 5.3%)	2.7% (1.7 to 3.8%)	1.55 (1.20 to 2.00)
Cetuximab	3	62/1,779	39/1,803	3.8% (1.1 to 6.5%)	2.3% (0.5 to 4.1%)	1.60 (1.08 to 2.37
Panitumumab	5	83/1,753	52/1,693	4.8% (3.2 to 6.5%)	2.8% (2.0 to 3.6%)	1.51 (1.08, 2.13)
Colorectal cancer	5	86/2,381	55/2,400	4.1% (1.2 to 6.9%)	2.5% (1.2 to 3.8%)	1.57 (1.12 to 2.18)
Gastroesophagealcancer	1	27/446	16/436	6.1% (3.8 to 8.3%)	3.7% (1.9 to 5.4%)	1.65 (0.90 to 3.02)
NSCLC	1	30/660	19/616	4.2% (2.5 to 5.9%)	2.8% (1.5 to 4.2%)	1.47 (0.79 to 2.76)
Biliary tract cancer	1	2/45	1/44	4.6% (0 to 10.6%)	2.4% (0 to 6.8%)	1.96 (0.18 to 20.80)

Subgroups analyses

Tables 2 shows results by anti-EGFR agent used, anti-EGFR dose and underlying malignancy (Table 2). The effect size varied, but the differences among subgroups were not statistically significant.

Influence of anti-EGFR scheduled dose on RR of VTE and PE

We explored whether the use of non-standard schedule of cetuximab or panitumumab may influence the risk of thromboembolism. We categorized as "standard" the recommended schedule of 400 mg/m^2 initial dose followed by 250 g/m^2 weekly for cetuximab and 6 mg/kg bi-weekly for panitumumab. Four studies[35,41,44,45] reported different schedules (Table 1). No statistically significant difference between subgroups was found (Supporting Information Appendix). The reported data did not permit reliable exploration of dose-response relationship or threshold effect.

Influence of kind of anti-EGFR agent

For the cetuximab trials the average VTE weighted mean incidence was 6.1% (95% CI 4.5 to 7.6%) in patients receiving cetuximab regimens and 3.7% (95% CI 2.7 to 4.7%) in patients receiving corresponding regimens without cetuximab. In the panitumumab subgroup weighted mean incidence was 10.7% (6.1 to 15.4%) in patients receiving panitumumab regimens and 6.5% (95% CI 3.3 to 9.6%) in patients receiving the same regimens minus panitumumab. Using the fixed-effect model the RR of VTE was 1.46 (95% CI 1.20 to 1.79) in cetuximab subgroup and 1.46 (95% CI 1.18 to 1.80) in the panitumumab subgroup (Table 2), with no statistically significant difference between the two subgroups (Fig. 3).

In the cetuximab subgroup we found a PE weighted mean incidence of 3.8% (95% CI 1.1 to 6.5%) VS 2.3% (95% CI 0.5 to 4.1%) (Table 2). In the panitumumab subgroup the weighted mean incidence was 4.8% (95% CI 3.2 to 6.5%) VS 2.8% (95% CI 2.0 to 3.6%). Using the fixed-effect model the RR of PE was 1.60 (95 CI % 1.08 to 2.37) in cetuximab subgroup and 1.51 (95% CI 1.08, 2.13) in the panitumumab subgroup (Table 2). No statistically significant difference between subgroups was detected (Fig. 4). F4

Influence of underlying tumour type

Given the potentially differing underlying risks of VTE and PE among patients with different tumour types, an exploratory analysis stratifying patients by type of malignancy was performed (Table 2). We found that the majority of the evidence is provided by studies in colorectal cancer patients. Although effect sizes and incidences for both VTE and PE were variable, no statistically significant differences between types of tumour were observed, Thus the most reliable estimate of effect is the overall RR 1.45 for VTE and 1.56 for PE (Table 2; Supporting Information Appendix).

Sensitivity analyses

Sensitivity analyses were carried out to define whether co-administration of Bevacizumab might have affected

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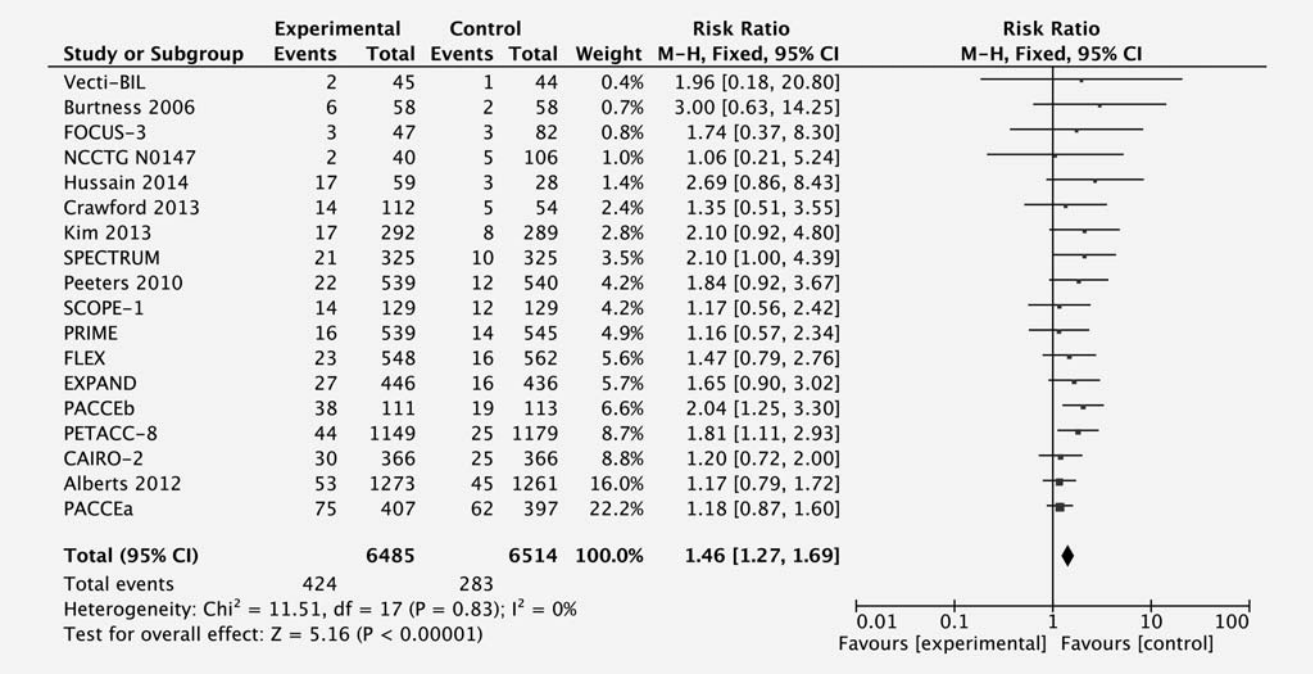

Figure 3. Overall Relative risk of VTE. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

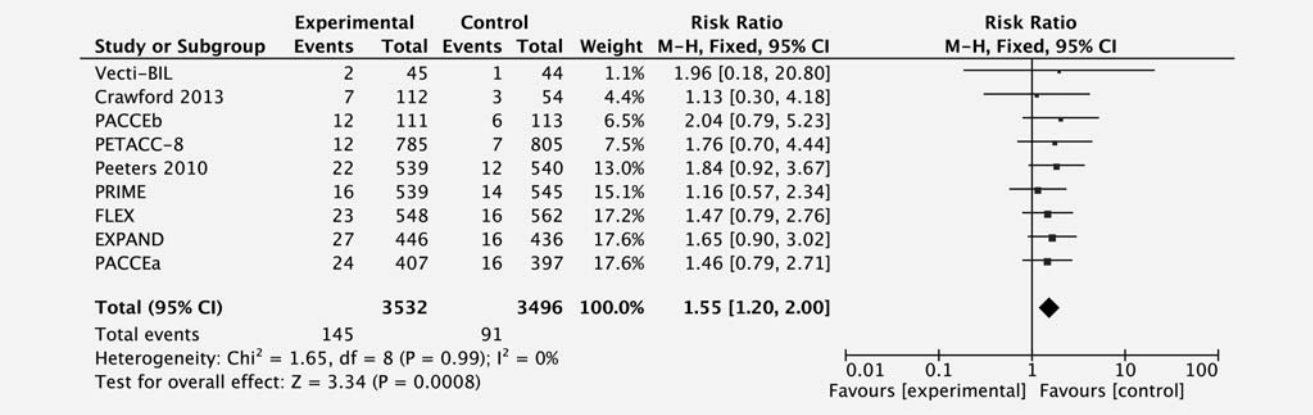

Figure 4. Overall Relative risk of PE. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

heterogeneity. No significant change was noted in RR of VTE and PE (see Supporting Information Appendix).

We also explored clinical heterogeneity by carrying out sensitivity analyses based on imbalance in treatment duration between two arms of each study, as reported by the authors. We excluded those RCTs in which a statistically significant difference ($p < 0.05$) in treatment duration was reported; the results were consistent with those of the primary analyses (see Supporting Information Appendix). However, differences in treatment duration were reported only for a minority of the studies included, and consequently this analysis remains very uncertain.

Publication bias

We found no obvious evidence of bias related to small study size, such as publication bias. Visual inspection of funnel plots for both VTEs and PE (see Supporting Information Appendix) did not reveal substantial asymmetry, even though only a part of the potentially eligible studies reported severe thromboembolic events.

Discussion

Cancer-associated thromboembolism is a substantial problem in clinical practice. It is considered a common, if not the most common, cause of death in patients with solid tumors.[3,4] Drug-exposure can increase such risk.[46]

Several mechanisms have been proposed to explain the hypercoagulable state of cancer patients treated with anticancer drugs. Experimental studies have indicated that the endothelium of fluorouracil-treated animals can be badly damaged, resulting in denudation of underlying structures, with consequential

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platelets accumulation and fibrin formation. Moreover, in humans exposed to fluorouracil treatment a significant increase in the level of fibrinopeptide A (a substance associated with hypercoagulable states released from the amino-terminal ends of fibrinogen) has been reported.[47] While it had been demonstrated that chemotherapy can also induce platelet activation, upregulation of prothrombotic factors and, in particular, endothelial injury[48] the pathogenesis of the thrombotic events associated with anti-EGFR MoAbs remains unclear, although potential mechanisms can be hypothesized.

The role of EGFR blockade in directly inducing endothelial damage or increasing thrombogenicity has not been proved. An enhancement in the expression of plasminogen activator was observed *in vitro* in human microvascular endothelial cells exposed to EGF,[49] but it appears more plausible that anti-EGFR MoAbs could prolong the uncovering of endothelial structures resulting from co-administered agents, favouring platelet activation, leukocyte adhesion, oxidative stress, coagulation and inflammation, all factors leading to thromboembolism.[50] It is well-known that EGF normally act as mitogens stimulating growth of various populations of cells including the endothelial ones.[51] The blockade of EGFR activation, by either tyrosine kinase inhibitors or antibodies, causes a dose-dependent decrease of the angiogenesis related factors VEGF, Transforming Growth Factor-α (TGF-α), basic Fibroblast Growth Factor (bFGF), and IL-8 in tumour cells, resulting in the modulation of angiogenesis.[52–55] It seems that EGF may also affect angiogenesis independently of other angiogenic factors. Hirata and colleagues inhibited EGF-induced angiogenesis *in vitro* by using an EGFR-antagonist, but obtained only a partial inhibition using a VEGFR-inhibitor.[56]

We sought to comprehensively examine the relationship between anti-EGFR MoAbs-based regimens and risk of VTEs and PE in patients with cancer by conducting a systematic review and combining results from eligible RCTs in a series of meta-analyses.

Based on information from 12,870, patients enrolled in 17 RCTs, we found that those treated with anti-EGFR MoAbs-containing regimens were approximately 1.5 times more likely to experience VTE or PE, compared to those treated with the same regimens without anti-EGFR MoAbs. It is notable that every single trial showed more VTEs and PEs in the MoAbs arms (as shown by all falling on the right hand side of the line of equivalence in Figs. 4 and 5). F5

In line with a large meta-analysis of clinical studies[57], our sensitivity analysis, excluding patients receiving anti-VEGFR MoAb bevacizumab, did not modify the risk of thromboembolic events. Although incidence of VTE and PE varied among patients with different types of tumours, the impact of anti-EGFR MoAbs on the relative risk of VTEs and PE did not differ significantly between malignancies. Similarly, we found higher incidence values in the panitumumab subgroup compared to the cetuximab subgroup, but RRs were very similar.

It is noteworthy that while in the panitumumab Group 4 comparisons out of 5 are based on metastatic colorectal cancer patients, in the cetuximab group, more than the half (6 out of 11) of the studies enrolled patients with malignancies other than colorectal cancer, and only 4 enrolled participants with metastatic diseases. This condition could be associated with a higher baseline thromboembolic risk. We found an overall weighted mean incidence of 10.9% in metastatic cancer patients receiving cetuximab.

Strengths and limitations

To the best of our knowledge, this is the largest and most-up-to-date systematic review evaluating the risk of VTEs in cancer patients and the first providing a specific analysis on the risk of PE induced by cetuximab and panitumumab. We took a wider perspective including eleven additional studies and consequently a larger population than a previously published meta-analysis.[17] Furthermore, with the aim of reducing confounding factors, we included only studies where cetuximab or panitumumab were administered in addition to exactly the same regimen used in the control arm.

As with other systematic reviews and meta-analyses, there were differences between included trials in terms of population, underlying malignancy, intervention, and duration of follow-up. The risk of bias of the included studies varied from low to high (Fig. 2). All trials had a high risk of performance and detection bias related to the lack of blinding (which is usual in cancer clinical trials). However, this has limited relevance and impact for the outcomes of interest as grade 3–4 AEs require medical intervention or hospitalization and are unlikely to be misdiagnosed. There was no clear evidence of bias related to small study size, such as publication bias.

It is notable that only a fraction 17 (out of 45) of the otherwise eligible trials identified by our searches reported thromboembolic events, such finding could represent a bias, although it may be due to the fact that the occurrence of thromboembolic events was not a primary end-point in RCTs which focused on effectiveness outcomes, that no such events were observed, or that authors did not report all the events observed during a trial. This seems to be the case in at least eleven of the twenty-nine excluded articles, in which only the most frequent AEs (with a threshold ranging from 2% to 10%) were reported (see Supporting Information Appendix).

Patients enrolled into randomized phase II and III trials meet rigorous eligibility criteria, which exclude many patients at higher risk for thromboembolism which may have resulted in a lower incidence of anti-EGFR MoAbs-associated thromboembolic events than in the wider cancer population. Nonetheless selective underreporting cannot be ruled out.

In conclusion, the additional risk of thromboembolic events should be taken into account in decision-making. Clinicians should assess baseline thromboembolic risk[58,59] and consider the additional risk related to the addition of anti-EGFR, taking into account current evidence[60,61] on benefit of antithrombotic prophylaxis, when deciding whether to add cetuximab or panitumumab to other anti-cancer agents. Prevention of VTE in cancer patients is a major challenge particularly because of the potential additional risks relating to use of anti-cancer drugs.

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Further investigation of anti-EGFR MoAb in cancer is needed to better define relationships between these agents and the risk of severe and life-threatening thromboembolism to develop risk-reduction strategies optimizing the benefit-harm ratio of anti-EGFR MoAbs.

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