Risk of venous thromboembolism with the erythropoiesis-stimulating agents (ESAs) for the treatment of cancer-associated anemia: a meta-analysis of randomized control trials

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Background: In anemic patients receiving myelosuppressive chemotherapy, erythropoiesis-stimulating agents (ESAs) raise hemoglobin levels and reduce transfusion requirements, but ESA-related safety concerns exist. To evaluate the overall risk of venous thromboembolism (VTE) associated with the use of ESAs, a systematic review and meta-analysis of published randomized controlled trials (RCT) was performed.

Methods: The databases of PubMed and Web of Science were searched from January 1966 until December 2012 and abstracts presented at American Society of Clinical Oncology conferences held between January 2000 and December 2012 were searched to identify relevant clinical trials. Summary incidence rates, relative risks (RRs), and 95% confidence intervals (CIs) were calculated.

Results: Data from a total of 11,632 patients with cancer in 50 RCTs were identified and included for meta-analysis. Among those patients receiving ESAs, the summary incidences of all-grade VTE were 7.62%. Patients with cancer who received ESAs had increased VTE risks (482 events among 6,238 patients treated with ESA *vs.* 269 events among 5,394 control patients; RR=1.75; 95% CI, 1.49-2.05). The highest risk of VET was found in patients with ovarian and cervical cancer for 2.45 (1.12-5.33).

Conclusions: The use of ESAs was significantly associated with an increased risk of developing VTE in cancer patients receiving this drug. The risks of VTE may vary with various tumor types.

Key Words: Erythropoiesis-stimulating agents (ESAs); venous thromboembolism (VTE); meta-analysis; randomized controlled trials (RCT)

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Introduction

Anaemia is a common occurrence in patients with cancer, arising either as a result of the underlying malignant disease, as a consequence of myelosuppressive chemotherapy or radiotherapy, or a combination of both (1). Anaemia is associated with a multitude of symptoms including fatigue, dyspnea, depression, and other co-morbidities that have a profound impact on a patient's condition and quality of life (QoL) (2). Furthermore, a meta-analysis of 60 published studies suggested that anaemia may be an independent prognostic factor for survival in patients with cancer (3).

The Erythropoiesis stimulating agents (ESAs), erythropoietin and darbepoetin, are widely used to treat anemia in patients with cancer. Most randomized trials and previous meta-analyses have shown that ESAs increase haemoglobin concentrations, reduce the need for transfusions (4-6), and reduce fatigue (7). However, they have been reported to increase the risk of venous thromboembolism (VTE) (5,8) and might stimulate tumour growth (9). Their safety has been discussed repeatedly at

hearings of the US Food and Drug Administration and the European Medicines Agency (10,11).

Although two previous meta-analysis (5,8) reported that ESAs administration to patients with cancer was associated with increased risks of VTE, they did not conducted the subgroup analysis by stratified with study characteristics such as cancer types and hemoglobin level at baseline or target-line. Since then, several more large randomized clinical trials (RCTs) have been published. We therefore performed an updated meta-analysis of the ESA Phase III clinical trial experience to ascertain whether administration of ESAs increased the risk of VTE in patient with cancer and stratified by various cancer types.

Materials and methods

Publication search

The electronic databases PubMed and Web of Science were searched for studies to include in the present meta-analysis. An upper date limit of Dec 01, 2012 was applied; we used no lower date limit. Keywords included in our search were "Erythropoietin", "Darbepoetin", "cancer", and was limited to "randomized controlled clinical trials".

Abstracts and virtual meeting presentations containing the term "Erythropoietin" or "Darbepoetin" from the American Society of Clinical Oncology conferences (http://www.asco.org/ASCO) between January 2000 and Dec 2012 were also referenced to identify relevant clinical trials. Our initial selection of articles relied on careful reading of abstracts. We also reviewed the Cochrane Library for relevant articles. The references reported in the identified studies were also used to complete the search. When the same patient population was used in several publications, only the most recent, largest or complete study was included in this meta-analysis.

Study selection

The goal of this study was to evaluate the risk of VTE with ESAs for the treatment of cancer-associated anemia. Therefore, we selected for analysis only those randomized clinical trials that directly compared patients with cancer treated with and without ESAs. Phase I and single-arm phase II trials were excluded due to their lack of control groups. Specifically, clinical trials that met the following criteria were included in the meta-analysis: prospective phase II and III randomised clinical trials in patients with cancer; random assignment of participants to ESAs treatment or control/placebo in addition to concurrent chemotherapy and/or radiotherapy; and available data including event or incidence of VTE and sample size for analysis. Trials with uncertain or marked inequality of characteristics between groups at baseline were also excluded. Two reviewers (P.Z and Q.W) independently determined study eligibility. Disagreements were resolved by consensus.

Data extraction

Data extraction was performed based upon patient characteristics, treatment information, results, and follow-up from these selected trials. Incidences of VTE were extracted from the safety profile in each trial. Two reviewers extracted the data independently (P.Z and Q.W). Any discrepancies between reviewers were resolved by consensus. VTE in these studies was assessed and recorded according to the National Cancer Institute's common toxicity criteria (version 2 or 3; http://ctep.cancer.gov), which has been widely adopted in cancer clinical trials.

Statistical analysis

The overall the relative risks (RRs) for VTE and 95% confidence intervals (CIs) were calculated using Reviewer Manager Version 5.0 provided by the Cochrane Collaboration (12). For the meta-analysis, we used fixed-effects (weighted with inverse variance) or random effects model (13). For each meta-analysis, the Cochran's Q statistic and I^2 score were first calculated to assess the heterogeneity among the proportions of the included trials (14). For the P value of Cochran's Q statistic <0.1, the assumption of homogeneity was deemed invalid, and a random-effects model was reported. The causes of heterogeneity were also explored in this context. Otherwise, results from the fixed-effects model were reported. A two-tailed P value <0.05 was judged as statistically significant. We used the Begg's and Egger's tests to determine the presence of publication bias regarding primary endpoint (RR of high-grade hypertension) (15,16). A two-tailed P value of <0.05 was considered statistically significant.

Results

Study characteristics

Our search yielded a total of 368 potentially relevant clinical studies on ESAs and treatment of cancer in the literature

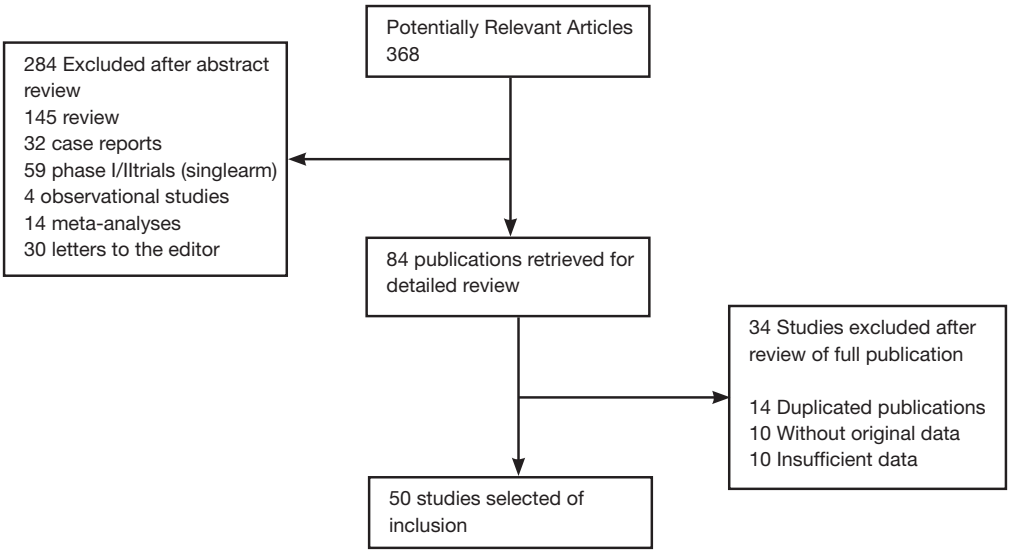

Figure 1 Search strategy and selection of trials with the venous thromboembolism outcomes

(*Figure 1*). After excluding review articles, phase I studies, single-arm phase II studies, case reports, meta-analyses, and observational studies (*Figure 1*), 50 phase III randomized controlled clinical trials (10,17-60) were included in our meta-analysis. *Table 1* presents the principal characteristics of these studies including study-year, drug, patient numbers, treatment duration, concomitant treatments, and cancer types. Epoetin alfa or epoetin beta was evaluated in 43 trials with 8,723 patients and darbepoetin in 7 trials with 2,909 patients. Duration of ESA treatment ranged from 4 to 52 weeks. Concomitant treatment varied between trials as follows: chemotherapy (29 trials), radiotherapy (3 trials), chemoradiotherapy (9 trials), palliative radiotherapy (1 trial), no treatment (4 trials), and treatment not reported (4 trials). Twenty-eight trials included 8,184 patients with a single cancer diagnosis (lung cancer (8 trials), breast cancer (6 trials), head and neck cancer (4 trials), cervical cancer (3 trials), ovarian cancer (4 trials), lymphoma (1 trial), CLL (1 trial) and multiple myeloma (1 trial)).

RR of venous thromboembolism

A meta-analysis was performed to calculate the overall RR of VTE (combination of all grade) associated with ESAs in comparison with controls for 50 trials included 11,632 patients. Among those patients receiving ESAs, the summary incidences of all-grade VTE were 7.62%. These trials identified a significantly increased risk of VTE among patients treated with ESA (482 events among 6,238 patients treated with ESA *vs.* 269 events among 5,394 control patients; RR=1.75; 95% CI, 1.49-2.05) (*Figure 2*), suggesting a 75% greater risk for developing VTE with ESAs compared with a control. This association also was not dominated by a small number of trials. There was no significant heterogeneity when evaluating all 50 trials (heterogeneity: Chi^2=37.02; I^2=0%; P=0.82).

Venous thromboembolism risk and tumor type

We have further determined the risk of VTE with ESAs separately according to their histology to investigate the relationship between tumor type and VTE. The incidence and risks of VTE with ESAs vary among different tumor types (*Table 2*). The highest incidence in ESAs and control was observed among patients with lung cancer (*Figure 3*) (18.34% and 12.14%); meta-analysis showed that the RR of VTE was 1.67 (1.31-2.12). The highest RR of VET was found in patients with ovarian and cervical cancer (*Figure 4*) for 2.45 (1.12-5.33), however the incidence was relative lower for (4.69% and 1.86%); While for patients with breast cancer (*Figure 5*), the RR of VTE was 1.84 (1.34-2.52), the incidence of VTE was 8.50% *vs.* 4.71%; For patients with head and neck cancer, the RR of VTE was relative higher with 2.14 (0.98-4.67), but was no significance statistically.

Publication bias

No evidence of publication bias was detected for the primary

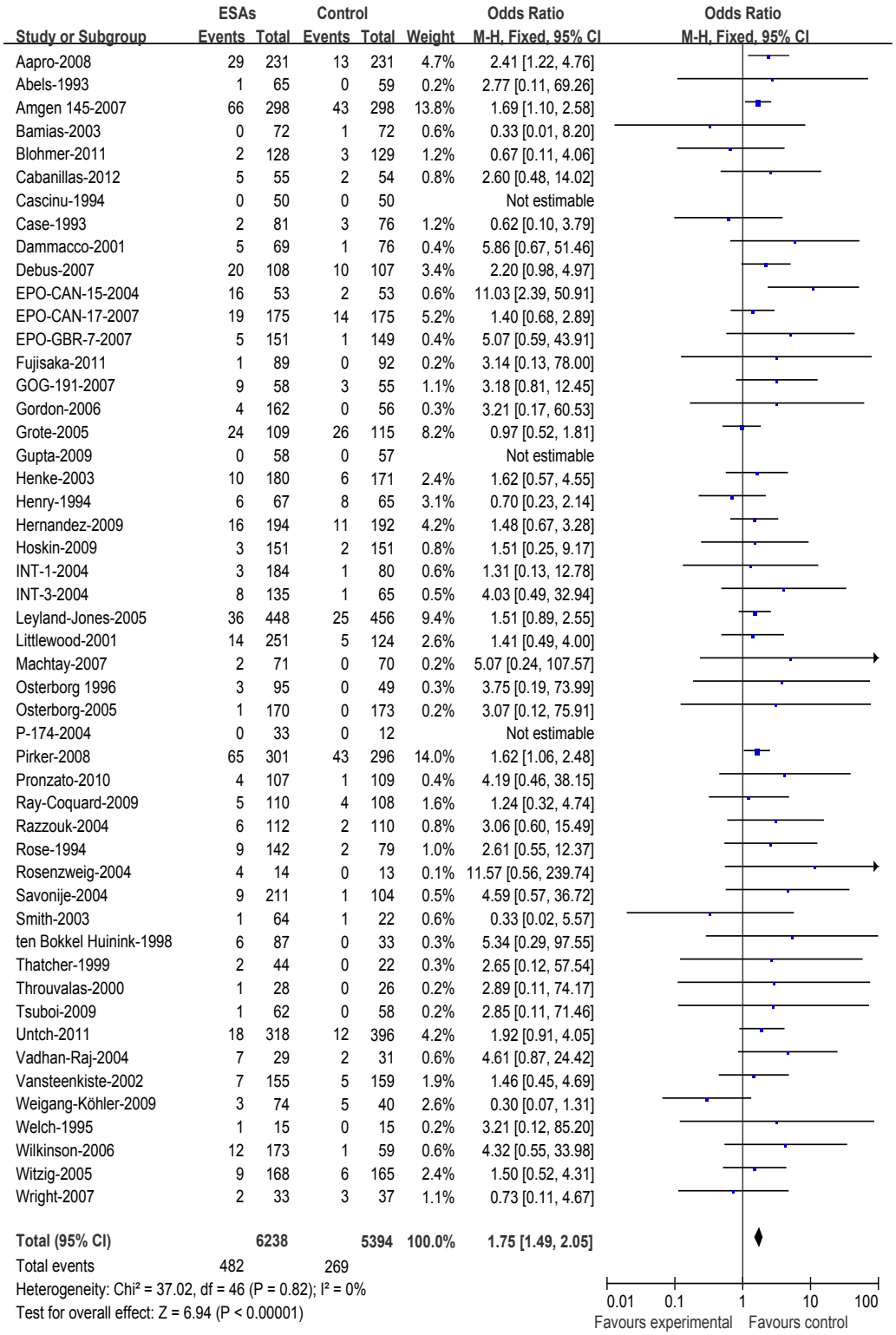

Figure 2 Meta-analysis of VTE rates in trials of ESAs *vs.* placebo or control overall tumor types. The size of the squares is proportional to the sample size and the number of events. Horizontal lines denote 95% confidence intervals (CIs). The diamond shows the confidence interval for the pooled relative risks. Positive values indicate a relative risk increase for VTE in patients receiving ESAs

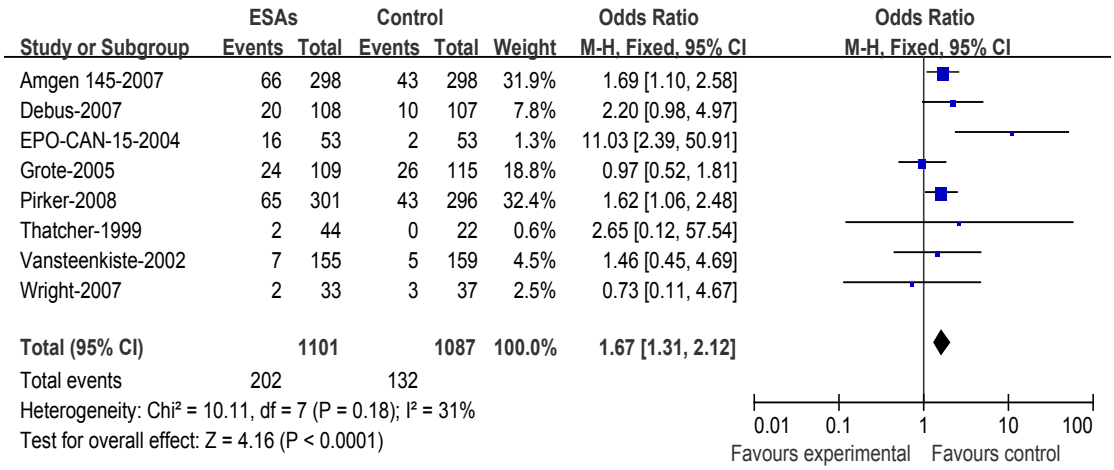

Figure 3 Meta-analysis of VTE rates in trials of ESAs *vs.* placebo or control in lung cancer

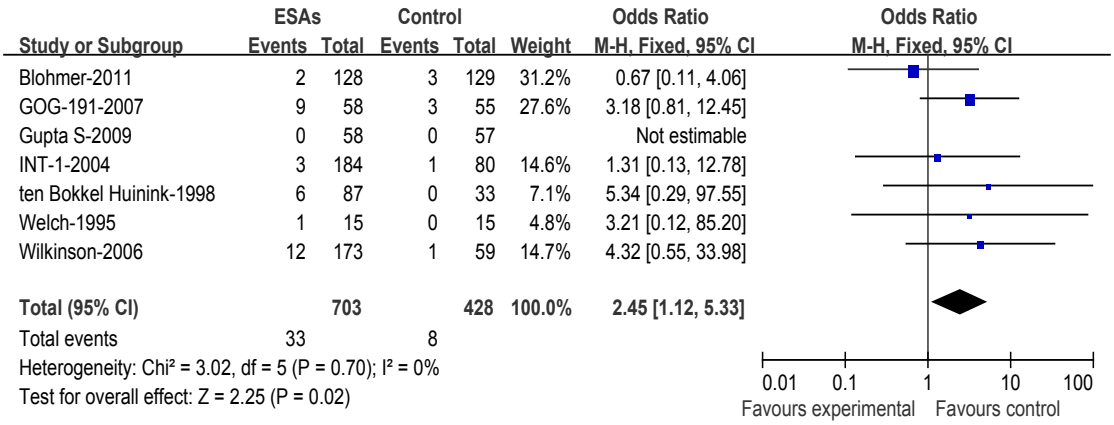

Figure 4 Meta-analysis of VTE rates in trials of ESAs *vs.* placebo or control in ovarian cancer and cervical

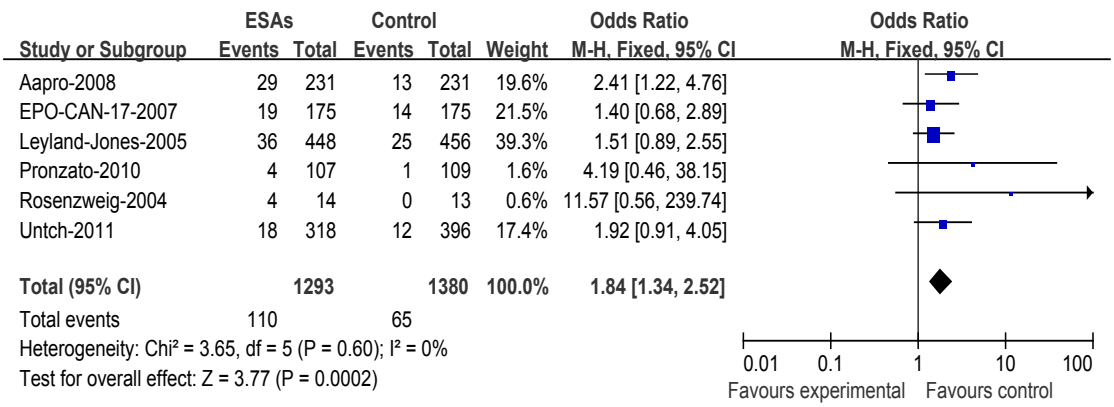

Figure 5 Meta-analysis of VTE rates in trials of ESAs *vs.* placebo or control in breast cancer

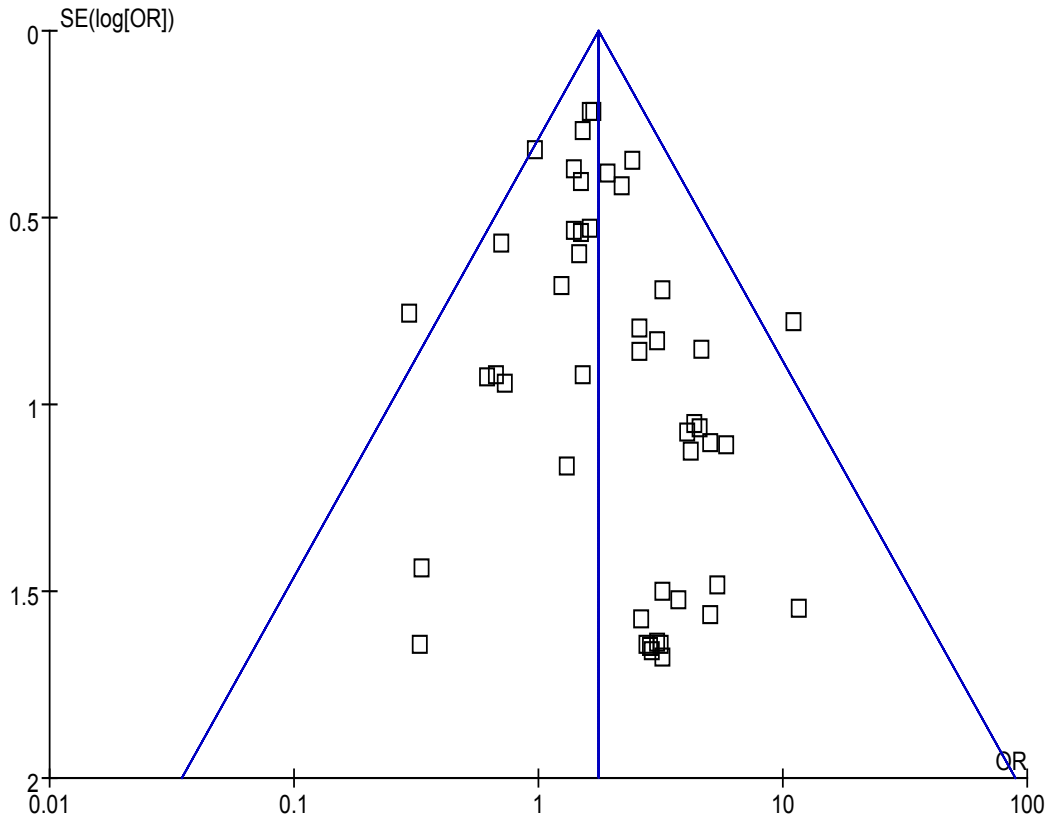

Figure 6 Funnel plot of the 50 evaluable trials assessing the risks of VTE and ESAs administration

end point of this study (RR of venous thromboembolism) by either the Begg or Egger test (Begg test, P=0.43; Egger test, P=0.59) (*Figure 6*).

Discussion

VTE is a major complication of cancer, and one of the leading causes of death in cancer patients (61). The association of VTE with ESAs presents a challenge for recognition because many RCTs may not be powered to reveal a significant relationship. In our meta-analysis, we involved 50 RCTs including a total of 6,238 cancer cases with ESAs and 5,394 patients with controls and demonstrated that ESAs are associated with a significantly increased risk of VET [RR=1.75 (95% CI, 1.49-2.05); P<0.00001] in patients with a variety of cancer types. The highest increased risk is observed in patients with ovarian and cervical cancer [RR=2.45 (95% CI, 1.12-5.33)]. The highest incidence of VTE in ESAs and control is observed among patients with lung cancer for 18.34% and 12.14%.

Our data were consistent with the results of a previous meta-analysis (8) published in 2008 that showed the increased risks of VTE in ESAs to patients with cancer. Bennett CL *et al.* study included only 38 studies, and the data were insufficient to determine the risks of VTE for subgroups divided according to types of cancer. We have improved upon that previous meta-analysis by including more recent related RCTs and by generally using a more comprehensive search strategy, screening and study selection, were performed independently and reproducibly by two re-viewers.

Expression of erythropoietin and erythropoietin receptors has been demonstrated in a variety of human cancers (62). Erythropoieitn stimulation of cancer cells *in vitro* activates signal transduction pathways, including phosphatidylinositol 3-kinase-Akt and JAK-STAT (Janus kinase Signal Transducer and Activator of Transcription) (63). In head and neck squamous cell carcinoma and melanoma, activation of the erythropoietin/erythropoietin receptor signaling axis results in measurable cellular effects, including proliferation, antiapoptosis, and invasion (64-66). Erythropoietin-mediated functions may result from autocrine/paracrine

Table 1 Characteristics of the 50 trials (11,632 patients) included in the meta-analysis

Study-year	Drug	No. of patients (ESA/Control)	Duration of treatment	Concomitant treatment	Types of cancer included
Aapro-2008	Epoetin beta	463 (231/231)	24 wks	Chemotherapy	metastatic breast cancer
Abels-1993	Epoetin alfa	413 (213/200)	8 wks	None	Any excluding primary myeloid malignancy or acute leukemia
Amgen 145-2007	Darbepoetin	583	24 wks	Chemotherapy	SCLC
Bamias-2003	Epoetin alfa	144 (72/72)	12 wks	Chemotherapy	Ovarian, NSCLC, SCLC, other
Blohmer-2011	Epoetin alfa	264 (128/129)	N/A	Chemoradiotherapy	cervical cancer
Cabanillas-2012	Epoetin alpha	109 (55/54)	N/A	Chemotherapy	acute lymphoblastic leukemia (ALL), lymphoblastic lymphoma (LL), or Burkitt lymphoma (BL)
Cascinu-1994	Epoetin alfa	100 (50/50)	9 wks	Chemotherapy	stomach, ovary, melanama, head and neck and lung
Case-1993	Epoetin alfa	157 (81/76)	12 wks	Chemotherapy	Various solid and nonmyeloid tumors
Dammacco-2001	Epoetin alfa	145 (69/76)	12 wks	Chemotherapy	MM
Debus-2007	Epoetin alfa	389	Terminated early for poor accrual	Chemoradiotherapy	NSCLC
EPO-CAN-15-2004	Epoetin alfa	106 (53/53)	12-24 wks	Chemoradiotherapy	Limited disease SCLC
EPO-CAN-17-2007	Epoetin alfa	354	28 wks max	Chemotherapy	Stages I-IV breast cancer
EPO-GBR-7-2007	Epoetin alfa	300 (151/149)	Terminated early for poor accrual	Radiotherapy	Head and neck,
Fujisaka-2011	Epoetin beta	181 (89/92)	12 wks	Chemotherapy	lung or gynaecological
GOG-191-2007	Epoetin alfa	113 (58/55)	N/A	Chemoradiotherapy	Cervix carcinoma
Gordon-2006	Darbepoetin	220	17 wks	None	Nonmyeloid malignancies
Grote-2005	Epoetin alfa	224 [109/115)	12 wks	Chemotherapy	SCLC
Gupta-2009	Epoetin beta	115 (58/57)	5 wks	Chemoradiotherapy	advanced cervical cancer
Henke-2003	Epoetin beta	351 (180/171)	7-9 wks	Radiotherapy	Advanced head and neck cancer
Henry-1994	Epoetinalfa	132 (67/65)	12 wks	Chemotherapy	Any excluding primary myeloid malignancy or acute leukemia
Hernandez-2009	Darbepoetin alfa	386 (193/193)	16 wks	Chemotherapy	lung, ovarian, cervical, Breast and others
Hoskin-2009	Epoetin alfa	300 (151/149)	N/A	Radiotherapy	Head and neck cancer
INT-1-2004	Epoetin alfa	244 (164/80)	1 mo after chemotherapy	N/A	Ovarian
INT-3-2004	Epoetin alfa	200 (135/65)	12 wks	N/A	Mixed
Leyland-Jones-2005	Epoetin alfa	939 (469/470)	52 wks	Chemotherapy	Metastatic breast cancer
Littlewood-2001	Epoetin alfa	375 (251/124)	28 wks	Chemotherapy	Various solid and nonmyeloid hematologic tumors
Machtay-2007	Epoetin alfa	148 (74/74)	9-10 wks	Chemoradiotherapy	Head and neck
Osterborg 1996	Epoetin beta	121 (82/39)	24 wks	Chemotherapy	MM, NHL
Osterborg-2005	Epoeitn beta	349	16 wks	Chemotherapy	NHL, CLL, MM
P-174-2004	Epoetin alfa	45 (33/12)	12 wks	N/A	CLL
Pirker-2008	Darbepoetin alfa	600 (301/299)	9 wks	Chemotherapy	Extensive-stage SCLC

Table 1 (Continued)

Table 1 (Continued)

Study-year	Drug	No. of patients (ESA/Control)	Duration of treatment	Concomitant treatment	Types of cancer included
Pronzato-2010	Epoetin alfa	216 (107/109)	4 wks	Chemotherapy	Breast cancer
Ray-Coquard-2009	Epoetin alfa	218 (110/108)	12 wks	Chemotherapy	Non-Hodgkin's lymphoma,
Razzouk-2004	Epoetin alfa	224 (113/111)	16 wks	Chemotherapy	Solid tumors, HD, NHL
Rose-1994	Epoetin alfa	221 (142/79)	12 wks	None	CLL
Rosenzweig-2004	Epoetin alfa	27 (14/13)	8 wks	N/A	metastatic breast cancer
Savonije-2004	Epoetin alfa	315 (211/104)	14 wks	Chemotherapy	Solid tumors
Smith-2003	Darbepoetin	86 (64/22)	12 wks	None	Genitourinary, breast, gastrointestinal, lymphoma, myeloma, chronic lymphocytic lymphoma, NHL
ten Bokkel Huinink-1998	Epoetin beta	122 (88/34)	24 wks	Chemotherapy	Ovarian carcinoma
Thatcher-1999	Epoetin alfa	64 (42/22)	26 wks	Chemotherapy	SCLC
Throuvalas-2000	Epoetin	55 (28/27)	6 wks	Chemoradiotherapy	Cervix and bladder carcinoma
Tsuboi-2009	epoetin beta	120 (62/58)	8 wks	Chemotherapy	Lung cancer or malignant lymphoma
Untch-2011	Darbepoetin alfa	714 (396/318)	N/A	Chemotherapy	primary breast cancer
Vadhan-Raj-2004	Epoetin alfa	60 (29/31)	16 wks	Chemoradiotherapy	Gastric or rectal cancer combined
Vansteenkiste-2002	Darbepoetin	320	12 wks	Chemotherapy	SCLC and NSCLC
Weigang-Köhler-2009	Epoetin alfa	114 (74/40)	12 wks	Chemotherapy	Ovary, Lung, Breast and others
Welch-1995	Epoetin alfa	30 (15/15)	18 wks	Chemotherapy	advanced ovarian carcinoma
Wilkinson-2006	Epoetin alfa	173 (114/59)	28 wks	Chemotherapy	Ovarian cancer
Witzig-2005	Epoetin alfa	344 (174/170)	16 wks	Chemoradiotherapy	Lung, breast, other
Wright-2007	Epoetin alfa	70 (33/37)	12 wks	Palliative radiotherapy	NSCLC

Abbreviations: CLL, chronic lymphocytic lymphoma; ESA, erythropoiesis-stimulating agent; HD, Hodgkin disease; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; VTE, venous thromboembolism. N/A, not applicable

Table 2 Relative risk (RR) of VTE with ESAs among patients with various tumor types

Tumor type	No. of studies	Events/total		Incidence (%)	RR (95% CI)
		ESAs	Control	ESAs/control	
Overall	50	482/6,238	269/5,394	7.72%/4.98%	1.75 (1.49-2.05)
Ovarian and cervical cancer	7	33/703	8/428	4.69%/1.86%	2.45 (1.12-5.33)
Breast cancer	6	110/1,293	65/1,380	8.50%/4.71%	1.84 (1.34-2.52)
Lung cancer	8	202/1,101	132/1,087	18.34%/12.14%	1.67 (1.31-2.12)
Head and neck cancer	4	20/553	9/541	3.61%/1.66%	2.14 (0.98-4.67)

signaling or recruitment of both endogenous and exogenous erythropoietin by the tumor (67,68). Clearly, many issues remain to be clarified regarding the specific actions of ESAs in human cancer cells. Further research is needed to clarify cellular and molecular mechanisms and pathways of the effects of ESAs on thrombogenesis and their potential effects on tumour growth.

Our study has the following limitations. First, we could

not detect the association with the available data between the relative risk for VTE events and hemoglobin level at baseline or target line. Second, there was lack of standard definitions of VTE. It does not distinguish distal from proximal VTE, and accidental finding of VTE. Also, the majority of trials included in this meta-analysis reported VTE events in combined grades; in addition, the ability to detect VTE may vary among institutions in which these trials were performed, and may cause bias of the reported incidence rates. Third, the study may have a potential publication bias even though it was not detectable by our analysis. Fourth, this is a meta-analysis at the study level, and confounding factors at the patient level cannot be properly assessed and incorporated into the analysis. Finally, we did not report separately on epoetin *vs.* darbepoetin, because the American Society of Clinical Oncology/ American Society of Hematology guidelines considered the products as belonging to a single class (69).

In conclusion, our study has shown that the ESAs are associated with a significantly increased risk of VTE in cancer patients who receive chemotherapy and/or radiotherapy. The risks of VTE may vary with tumor type. It is imperative for physicians and patients to recognize the risk. In the event of VTE, a nticoagulation is indicated, and ESAs may be continued if benefits of the drug outweigh the risk. Future studies are needed to investigate the prevention and management of VTE associated with ESAs.

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