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ORIGINAL RESEARCH

Risk of venous and arterial thromboembolic events associated with anti-VEGF agents in advanced non-small-cell lung cancer: a meta-analysis and systematic review

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Aims: To assess the incidence and risk of arterial and venous thromboembolic events (ATEs and VTEs) associated with antivascular endothelial growth factor (VEGF) agents, including VEGF receptor-tyrosine kinase inhibitors and VEGF monoclonal antibodies, in advanced non-small-cell lung cancer (NSCLC) patients.

Methods: We performed a broad search of PubMed for relevant trials. Prospective randomized trials evaluating therapy with or without anti-VEGF agents in patients with advanced NSCLC were included for analysis. Data on VTEs and ATEs were extracted. The overall incidence, Peto odds ratio (Peto OR), and 95% confidence intervals (CIs) were pooled according to the heterogeneity of included trials.

Results: A total of 13,436 patients from 23 trials were included for analysis. Our results showed that anti-VEGF agents significantly increased the risk of developing high-grade ATEs (Peto OR: 1.44, 95% CI: 1.00–2.07, P=0.048), but not for all-grade ATEs (Peto OR: 0.94, 95% CI: 0.56–1.59, P=0.82) compared with controls. Additionally, no increased risk of all-grade and high-grade VTEs (Peto OR: 0.94, 95% CI: 0.67–1.31, P=0.71 and Peto OR: 0.95, 95% CI: 0.73–1.22, P=0.67, respectively) was observed in advanced NSCLC patients receiving anti-VEGF agents.

Conclusion: The use of anti-VEGF agents in advanced NSCLC patients significantly increased the risk of high-grade ATEs, but not for VTEs. Clinicians should be aware of the risk of severe ATEs with administration of these drugs in advanced NSCLC patients.

Keywords: anti-VEGF agents, toxicity, arterial thromboembolic events, venous thromboembolic events, meta-analysis

Introduction

Angiogenesis, the formation of new blood vessels, is critical for tumor progression, invasion, and metastasis in many solid tumors.[1–3] Basic research shows that this process is mainly driven by vascular endothelial growth factor (VEGF), and thus angiogenesis inhibitors targeting the VEGF signal pathway are a potential treatment options for solid tumors.[4,5] In the past two decades, many novel anti-VEGF agents, including VEGF monoclonal antibodies and multitarget VEGF receptor (VEGFR)-tyrosine kinase inhibitors (TKIs)/monoclonal antibodies, have been proven to improve survival benefits in many solid tumors including non-small-cell lung cancer (NSCLC). Until now, three anti-VEGF agents, including bevacizumab, ramucirumab, and nintedanib, have been approved by the US Food and Drug Administration (FDA) for the treatment

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of advanced NSCLC,[6–9] and it is anticipated that the use of these agents in cancer patients would be increased in the near future.

However, the VEGF signal pathway plays a critical role in physiological functions and homeostasis in the cardiovascular and renal systems. Previous research has found that VEGF is of great importance to regulate angiogenesis and the vascular tone.[10] Other vascular proteins, such as tissue factor (TF) and endothelial nitric oxide synthase, have also been involved in controlling endothelial thrombogenicity and regulation of vascular tone. While TF and its distinct isoforms can induce the expression of VEGF, and interact with VEGF and its pro-/antiangiogenic isoforms could in turn leads to modifications of essential biological processes.[11] Thus, inhibition of angiogenesis pathway could cause a variety of adverse effects.[12] Indeed, a variety of toxicities associated with anti-VEGF signal pathway including hypertension,[13–17] proteinuria or renal dysfunction,[18–21] congestive heart failure,[22–25] hemorrhage,[26,27] and gastrointestinal perforation[28–30] have been reported in previous studies. Although several meta-analyses have been conducted to assess the risk of arterial and venous thromboembolic events (VTEs and ATEs) associated with anti-VEGF agents, all these studies include different tumor types.[31–38] It has been reported that some tumor-dependent intrinsic mechanisms have been related to VTEs or ATEs, and patient baseline characteristics differ between tumor types. Additionally, time to treatment failure and follow-up duration vary according to tumor types, and these factors are closely related to the likelihood of developing and detecting VTEs and ATEs. As a result, the risk of VTEs and ATEs associated with anti-VEGF agents in advanced NSCLC remains unknown. We thus conducted a meta-analysis of published trials to investigate the risk of ATEs and VTEs associated with the use of anti-VEGF agents in advanced NSCLC patients.

Methods

Data source

We performed this systematic review adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements.[39] We performed a board search of PubMed for relevant trials published between January 1, 1990 and November 31, 2015. The search included the following terms: "anti-VEGF agents", "VEGFR-TKIs", "bevacizumab", "aflibercept", "sorafenib", "sunitinib", "vandetanib", "pazopanib", "axitinib", "motesanib", "ramucirumab", "cediranib", "regorafenib", "cabozantinib", "brivanib", "tivozanib", "nintedanib", "angiogenesis inhibitors", "non-small-cell lung cancer", and "randomized clinical trial". Each publication was reviewed, and in case of duplicate publication only, the most complete, recent, and updated report of the clinical trial was included in the meta-analysis.

Inclusion criteria for our study were 1) patients having pathologically confirmed NSCLC, 2) trials comparing treatment with or without anti-VEGF agents, and 3) reporting data on VTEs or ATEs toxicity. We assessed the quality of reports of clinical trials by using the five-item Jadad scale including randomization, double-blinding, and withdrawals as previously described.[40]

Data extraction

Two independent investigators reviewed the titles and abstracts of potentially relevant studies. We retrieved the full text of relevant studies for further review by the same two reviewers. A third senior investigator resolved any discrepancies between reviewers. The same pair of reviewers extracted study details independently using a standardized pilot-tested form. A third investigator reviewed all data entries. We extracted the following information data: first author, study period, treatment regimens, sample size, number evaluable for toxicity, median age, median overall survival, and progression-free survival. We considered the following adverse outcomes as VTEs/ATEs: thrombosis/thrombus/embolism (excluded vascular access related-thrombosis if reported separately), arterial thrombosis, cerebral infarct, cerebral ischemia, cerebrovascular accident, myocardial infarction, and myocardial ischemia. We assessed and recorded adverse events according to the National Cancer Institute's common toxicity criteria (Version 2 or 3).[41]

Statistical analysis

Statistical analysis for overall risk of VTEs/ATEs was performed using comprehensive meta-analysis software Version 2.0 (Biostat, Englewood, NJ, USA). We used the Peto method to calculate odds ratios (ORs) and 95% confidence intervals (CIs) because this method provided the best CI coverage and was more powerful and relatively less biased than the fixed or random effects analysis when dealing with low event rates.[42] Between-study heterogeneity was estimated using the χ^2-based Q-statistic. Heterogeneity was considered statistically significant when $P_{\text{heterogeneity}} < 0.05$ or $I^2 > 50\%$.[43] Meta-analysis was performed using a random effects model in response to the expected clinical heterogeneity among the trials.[42] A two-sided P-value < 0.05 was considered

significant. The presence of publication bias was evaluated using the Begg and Egger tests.

Results

Search results

A total of 330 studies were identified from the database search, and 66 trials were retrieved for full-text evaluation. Forty-three trials were excluded for the reasons shown in Figure 1. Finally, a total of 13,436 patients from 23 randomized controlled trials were included for the meta-analysis.[6,8,9,44–63] The baseline characteristics of each trial are summarized in Table 1. Fifteen trials were performed in first-line settings and eight second-line settings. According to the inclusion criteria of each trial, patients were required to have an adequate renal, hepatic, and hematologic function. We roughly assessed the quality of each included study according to the Jadad score, and 14 trials had Jadad score of 5, and nine trials had Jadad score of 3.

Incidence of VTEs and ATEs

A total of 2,550 patients from eight treatment arms who received anti-VEGF agents were available for all-grade VTEs incidence analysis. Using a random effects model, the summary incidence of all-grade VTEs was 3.4% (95% CI: 2.0%–5.9%; Table 2). As for high-grade VTEs, a total of 6,900 patients from 21 treatment arms were included, and the pooled incidence was 1.8% (95% CI: 1.1%–2.9%; Table 2).

Four included trials reported the all-grade ATEs, and the pooled incidence was 2.1% (95% CI: 0.7%–6.0%; Table 2). As for high-grade ATEs, a total of 4,824 patients from 16 trials were included for analysis with a pooled incidence of 1.8% (95% CI: 1.2%–2.7%; Table 2) using a random effects model.

Peto odds ratio of VTEs and ATEs

A meta-analysis of the Peto OR for all-grade and high-grade VTEs attributable to anti-VEGF agents compared with controls was performed. The pooled results showed that the use of anti-VEGF agents did not increase the risk of all-grade (Peto OR: 0.94, 95% CI: 0.67–1.31, P=0.71; Figure 2) and high-grade VTEs compared with controls (Peto OR: 0.95, 95% CI: 0.73–1.22, P=0.67; Figure 3) using a fixed effects model. We then investigated the risk of ATEs associated with anti-VEGF agents. Our results showed that the use of anti-VEGF agents significantly increased the risk of high-grade ATEs (Peto OR: 1.44, 95% CI: 1.00–2.07, P=0.048; Figure 4) using a fixed effects model (I^2=32.1, P=0.11), whereas the use of anti-VEGF agents did not increase the risk of all-grade ATEs when compared to controls (Peto OR: 0.94, 95% CI: 0.56–1.59, P=0.82; Figure 5).

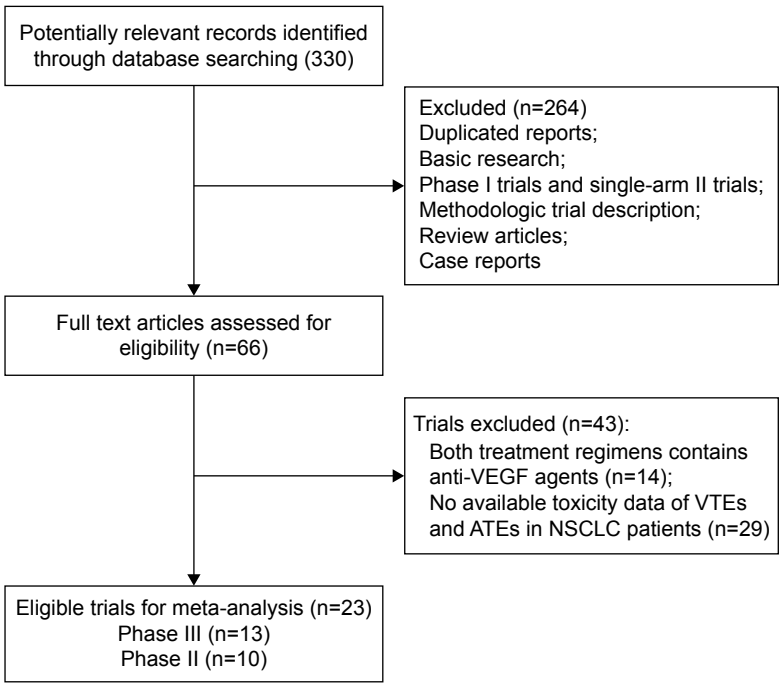

Figure 1 Selection process for randomized controlled trials included in the meta-analysis.
Abbreviations: VEGF, vascular endothelial growth factor; VTEs, venous thromboembolic events; ATEs, arterial thromboembolic events; NSCLC, non-small-cell lung cancer.

Table 1 Baseline characteristics of 23 included trials for analysis

Authors	Phase	Total patients	Therapy line	Treatment arms	Median age (years)	Median PFS, months	Median OS, months	Number for analysis	Jadad score
Johnson et al[63]	II	99	First-line	Bevacizumab 2.5 mg/kg/wk + PTX + CBP	NR	4.3	11.6	32	3
				Bevacizumab 5 mg/kg/wk + PTX + CBP	NR	7.4	17.7	34	
				PTX + CBP	NR	4.2	14.9	32	
Sandler et al[8]	III	878	First-line	Bevacizumab 5 mg/kg/wk + PTX + CBP	NR	6.2	12.3	427	3
				PTX + CBP	NR	4.5	10.3	440	
Heymach et al[61]	II	127	Second-line	Vandetanib 100 mg + Doc	61	4.4	13.1	42	5
				Vandetanib 300 mg + Doc	60	4	7.9	44	
				Placebo + Doc	58	2.8	13.4	41	
Herbst et al[62]	II	120	First-line	Bevacizumab 5 mg/kg/wk + chemotherapy	63.5	4.8	12.6	40	5
				Bevacizumab 5 mg/kg/wk + erlotinib	68	4.4	13.7	39	
				Placebo + chemotherapy	65	3	8.6	41	
Reck et al[60]	III	1,043	First-line	Bevacizumab 5 mg/kg/wk + GEM + DDP	59	6.7	NR	329	5
				Bevacizumab 2.5 mg/kg/wk + GEM + DDP	57	6.5	NR	330	
				Placebo + GEM + DDP	59	6.1	NR	327	
Herbst et al[57]	III	636	Second-line	Bevacizumab 5 mg/kg/wk + erlotinib	64.8	3.4	9.3	319	3
				Erlotinib	65	1.7	9.2	317	
Scagliotti et al[59]	III	926	First-line	Sorafenib 400 mg bid po + PTX + CBP	62	4.6	10.7	436	5
				Placebo + PTX + CBP	63	5.4	10.6	459	
de Boer et al[58]	III	534	Second-line	Vandetanib 100 mg + PEM	60	4.1	10.5	260	5
				Placebo + PEM	60	2.8	9.2	273	
Natale et al[56]	III	1,240	Second-line	Vandetanib 300 mg qd po	61	2.6	6.8	623	3
				Erlotinib	61	2	7.7	614	
Lee et al[55]	III	924	Second-line	Vandetanib 300 mg qd po	60	1.9	8.5	619	5
				Placebo	60	1.8	7.8	303	
Niho et al[54]	II	180	First-line	Bevacizumab 5 mg/kg/wk + PTX + CBP	61	6.9	22.8	119	3
				PTX + CBP	60	5.9	23.4	58	
Paz-Ares et al[53]	III	772	First-line	Sorafenib 400 mg bid po + GEM + DDP	60	6	12.4	385	5
				Placebo + GEM + DDP	58	5.5	12.5	387	
Scagliotti et al[51]	III	1,090	First-line	Motesanib 125 mg qd po + PTX + CBP	60	5.6	13	533	5
				Placebo + PTX + CBP	60	5.4	11	539	
Ramlau et al[52]	III	913	First-line	Aflibercept 6 mg/kg + Doc	59.6	5.2	10.1	456	5
				Placebo + Doc	59.6	4.1	10.4	457	
Groen et al[50]	II	132	Second-line	Sunitinib 37.5 mg qd po + erlotinib	59	2.8	8.2	65	5
				Placebo + erlotinib	61	2	7.6	67	
Belani et al[49]	II	170	First-line	Axitinib 5 mg bid po (continuous) + PEM + DDP	62	8	17	55	3
				Axitinib 5 mg bid po (modified) + PEM + DDP	62	7.9	14.7	58	
				PEM + DDP	59	7.1	15.9	55	

Garon et al[9]	III	1,253	Second-line	Ramucirumab 10 mg/kg + Doc	62	4.5	10.5	627	5	
				Placebo + Doc	61	3	9.1	618		
Gridelli et al[48]	II	124	First-line	Vandetanib 100 mg qd po + GEM	75	6.1	8.7	61	5	
				Placebo + GEM	75.48	5.6	10.2	63		
Laurie et al[48]	III	306	First-line	Cediranib 20 mg qd po + PTX + CBP	63	5.5	12.2	153	5	
				Placebo + PTX + CBP	62	5.5	12.1	153		
Reck et al[6]	III	1,314	Second-line	Nintedanib 200 mg bid po + Doc	60	3.4	10.9	652	5	
				Placebo + Doc	60	2.7	7.9	655		
Zinner et al[44]	II	361	First-line	PTX + CBP + bevacizumab followed by maintenance bevacizumab	65.4	5.49	11.7	179	3	
				PEM + CBP followed by maintenance PEM	65.8	4.44	10.5	182		
Doebele et al[45]	II	140	First-line	Ramucirumab 10 mg/kg + PEM + platinum	67	7.2	13.9	69	3	
				PEM + platinum	69	5.6	10.4	71		
Seto et al[46]	II	154	First-line	Bevacizumab 5 mg/kg/wk + erlotinib	67	16	NR	77	3	
				Erlotinib	67	9.7	NR	77		

Abbreviations: PTX, paclitaxel; CBP, carboplatin; DDP, cisplatin; GEM, gemcitabine; Doc, docetaxel; PEM, pemetrexed; PFS, progression-free survival; OS, overall survival; qd, quaque die; bid, bis in die; po, per os; wk, weekly; NR, not reported.

Publication bias

We used Begg's funnel plot and Egger's test to assess the publication bias of literatures. No evidence of obvious asymmetry was detected by Begg's test for VTEs (all-grade: P=0.62 and high-grade: P=0.80, respectively) and ATEs (all-grade: P=0.18 and high-grade: P=0.65, respectively). Similarly, Egger's test still did not suggest any evidence of publication bias for VTEs (all-grade: P=0.27 and high-grade: P=0.19, respectively) and ATEs (all-grade: P=0.08 and high-grade: P=0.11, respectively).

Discussion

Thromboembolic events are a major cause of morbidity and mortality in patients with advanced tumors.[64,65] Although the presence of malignancies itself and its associated physiologic changes are risk factors for thromboembolism, several anti-cancer therapies, including cytotoxic agents, angiogenesis inhibitors, and hormonal therapies, might increase the risk of developing a thromboembolic event.[66] During past decades, several anti-VEGF agents have been approved by the FDA for use in a variety of solid tumors due to its survival benefits; concerns have arisen regarding the risk of thromboembolic events with the use of these drugs. Previous meta-analyses consistently supported a significant increase in ATEs from both VEGFR-TKIs and bevacizumab across a range of advanced solid tumors. In one trial-level meta-analysis conducted by Choueiri et al[35] found that sunitinib or sorafenib treatment significantly increased the risk of ATEs (relative risk [RR] =3.03, P=0.015). Similarly, another individual patient-level meta-analysis (hazard ratio [HR]: 2.0, P=0.031)[37] and two trial-level meta-analyses (RR: 1.46, P=0.007 and RR: 1.44, P=0.013), respectively[67,68] also demonstrated that the risk of ATEs with bevacizumab and chemotherapy was higher than that in chemotherapy alone. A recent meta-analysis conducted by Qi et al[38] also found an increased risk of developing ATEs in cancer patients receiving VEGFR-TKIs (OR: 2.26, P=0.001). As far as we know, this was the largest study investigating the risk of VTEs and ATEs with anti-VEGF agents in advanced NSCLC patients with a total of 13,436 patients from 23 trials. In the present study, we found that the use of anti-VEGF agents significantly increased the risk of high-grade ATEs, but not for all-grade ATEs. As anti-VEGF agents are increasingly used in the treatment of advanced NSCLC patients, it is critically important for clinicians to be aware of the risk of ATEs associated with anti-VEGF agents and monitor and treat it appropriately.

Several studies have been conducted to investigate the risk of VTEs associated with anti-VEGF agents in cancer patients,

Table 2 Incidence of venous thromboembolic events (VTEs) and arterial thromboembolic events (ATEs) in advanced non-small-cell lung cancer patients receiving antivascular endothelial growth factor agents

Adverse events	Number of trials	Events	Total patients	I^2 (%)	Incidence (95% confidence interval)
VTEs					
All-grade	8	73	2,550	79.2	3.4 (2.0%–5.9%)
High-grade	21	143	6,900	83.2	1.8 (1.1%–2.9%)
ATEs					
All-grade	4	28	1,784	87.9	2.1 (0.7%–6.0%)
High-grade	16	79	4,824	60.6	1.8 (1.2%–2.7%)

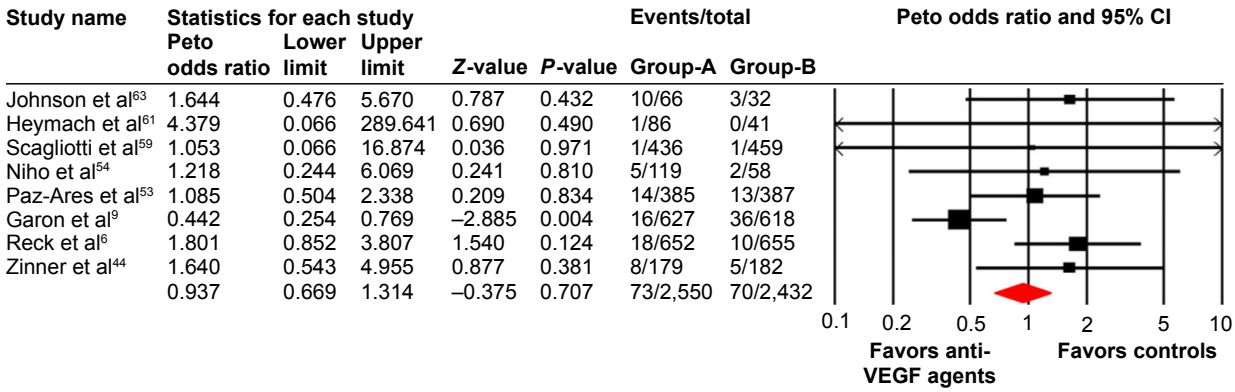

Figure 2 Odds ratio of all-grade venous thromboembolic events associated with antivascular endothelial growth factor (VEGF) agents vs control.
Notes: Group-A is the number of patients included for analysis in VEGF group; Group-B is the number of patients included for analysis in controlled group.
Abbreviations: CI, confidence interval; I^2, level of heterogeneity among included trials.

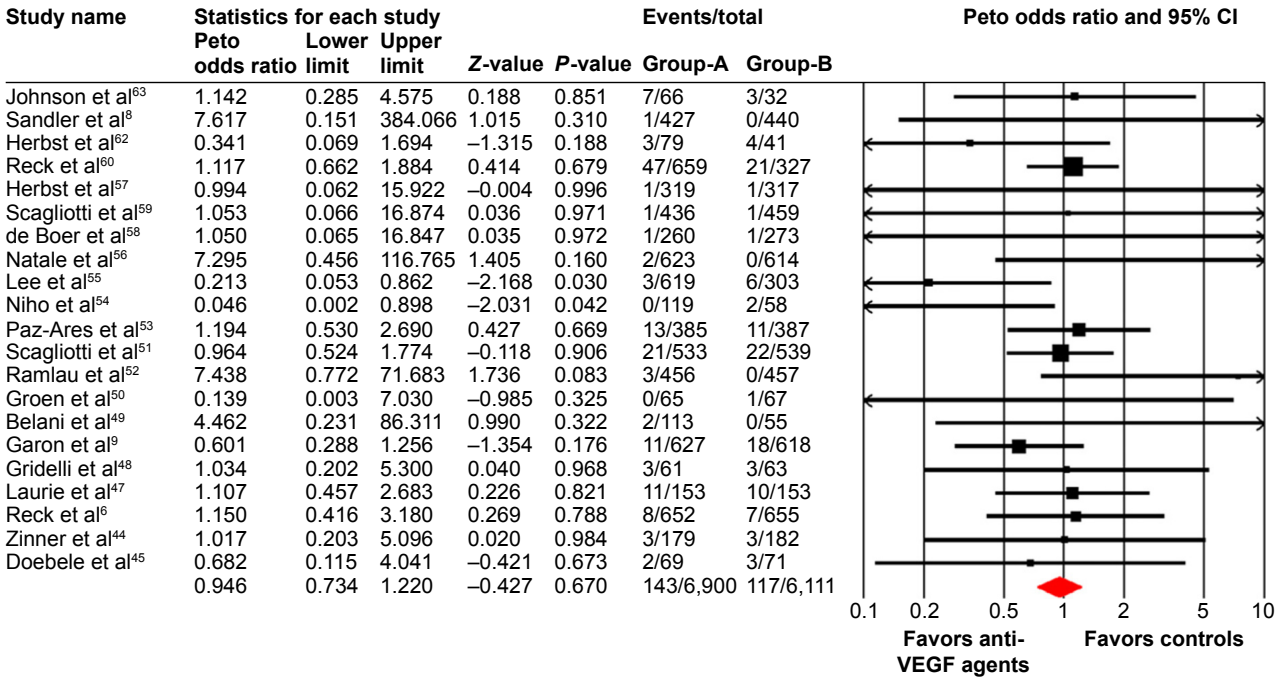

Figure 3 Odds ratio of high-grade venous thromboembolic events associated with antivascular endothelial growth factor (VEGF) agents vs control.
Notes: Group-A is the number of patients included for analysis in VEGF group; Group-B is the number of patients included for analysis in controlled group.
Abbreviation: CI, confidence interval.

Study name	Statistics for each study				
	Peto odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Johnson et al[63]	1.432	0.171	11.965	0.332	0.740
Sandler et al[8]	2.025	0.648	6.326	1.215	0.225
Herbst et al[62]	0.054	0.001	3.339	–1.388	0.165
Reck et al[60]	0.564	0.270	1.178	–1.525	0.127
Herbst et al[57]	5.239	1.592	17.245	2.725	0.006
Scagliotti et al[59]	2.065	0.555	7.675	1.082	0.279
Niho et al[54]	4.426	0.068	288.051	0.698	0.485
Scagliotti et al[51]	2.164	0.807	5.806	1.533	0.125
Ramlau et al[52]	7.422	0.464	118.833	1.417	0.157
Groen et al[50]	7.620	0.151	384.194	1.015	0.310
Garon et al[9]	0.738	0.258	2.117	–0.565	0.572
Gridelli et al[48]	7.764	0.480	125.582	1.443	0.149
Reck et al[6]	0.754	0.171	3.329	–0.373	0.709
Zinner et al[44]	7.514	0.149	378.730	1.008	0.313
Doebele et al[45]	2.091	0.544	8.036	1.074	0.283
Seto et al[46]	7.389	0.147	372.385	1.000	0.317
	1.441	1.003	2.070	1.978	0.048

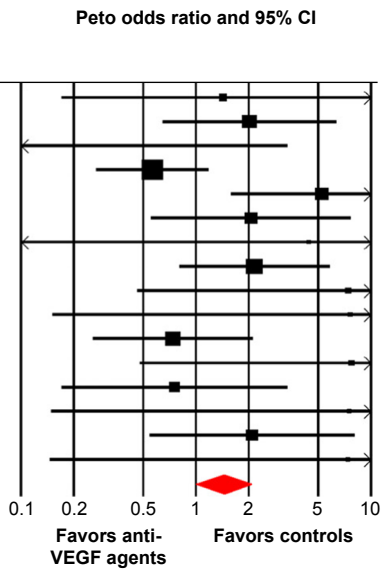

Figure 4 Odds ratio of high-grade arterial thromboembolic events associated with antivascular endothelial growth factor (VEGF) agents vs control.
Notes: Group-A is the number of patients included for analysis in VEGF group; Group-B is the number of patients included for analysis in controlled group.
Abbreviation: CI, confidence interval.

but the results are controversial. In one meta-analysis evaluating the impact of bevacizumab, the HR was 0.89 (P=0.44) and in the second study conducted by Hurwitz et al,[34] the OR was 1.13 (P=0.13). In a third trial-level meta-analysis (n=7,956), bevacizumab treatment significantly increases the risk of developing VTEs (RR: 1.33, $P<0.001$).[36] For VEGFR-TKIs and VTEs risk, two similar meta-analyses also found that the use of VEGFR-TKIs did not significantly increase the risk of VTEs (RR: 0.91, P=0.64 and RR: 1.10, P=0.64).[32,33] In the present study, we also found that anti-VEGF therapies did not significantly increase the risk of all-grade and high-grade VTEs when compared to controls. Based on our findings, NSCLC patients with a recent but controlled VTEs probably should not be denied an anti-VEGF agent.

The mechanism of causing thromboembolic events might be related to the anti-VEGF effect with anti-VEGF agents: the VEGF pathway regulates endothelial cell proliferation, survival, and helps maintain vascular integrity.[69] Inhibition of this pathway might lead to vascular wall defects and exposes procoagulant phospholipids.[70] Additionally, VEGF also increases the production of nitric oxide (NO) and prostacylin (PGI_2, prostaglandin I_2), and suppresses the pathways involved in the endothelial cell activation and apoptosis.[71] Hence, perturbation of endothelial cell function by inhibiting VEGF pathway may promote thromboembolism. Moreover, VEGF inhibition may also increase the expression of proinflammatory cytokines, causing damage and in situ thrombus formation.[72] Additionally, VEGF is known to affect the expression of TF, the primary initiator of blood coagulation. TF and its distinct isoforms (alternatively spliced [as]TF, and full-length [fl]TF) can induce the expression of and interact with VEGF and its pro-/antiangiogenic isoforms, which in turn leads to modifications of essential biological processes, such as thrombogenicity, angiogenesis, cell proliferation, tissue growth, and migration. [73] These processes as well as the interaction of VEGF with TF-associated pathways play

Study name	Statistics for each study				
	Peto odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Scagliotti et al[59]	1.477	0.473	4.612	0.671	0.502
Garon et al[9]	0.756	0.331	1.724	–0.666	0.505
Reck et al[6]	0.462	0.155	1.378	–1.385	0.166
Doebele et al[45]	2.426	0.673	8.741	1.355	0.175
	0.942	0.560	1.586	–0.224	0.823

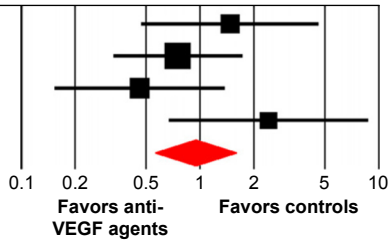

Figure 5 Odds ratio of all-grade arterial thromboembolic events associated with antivascular endothelial growth factor (VEGF) agents vs control.
Abbreviation: CI, confidence interval.

an essential role in cancer as well as in other diseases such as cardiovascular disease.[74] Goldin-Lang et al[75] showed that the expression of asTF and flTF was increased in NSCLC patients. This was associated with increased risk of thrombotic events in these patients.[75]

Limitations

Several limitations in our analysis need to be acknowledged. First, our study is a meta-analysis of published data, and we lack individual patient information. Therefore, intervening variables at the patient level are unavailable in the analysis. Second, toxicity data in randomized controlled trials have been reported to be suboptimal and variable as toxicity is usually not the primary outcome measure. Third, different anti-VEGF agents are included for analysis in the meta-analysis, which increases the clinical heterogeneity of the meta-analysis. Finally, the study might have a potential publication bias even though we detected no publication bias using the Begg and Egger tests.

Conclusion

Treatment with anti-VEGF agents in advanced NSCLC patients is associated with a significantly increased risk of high-grade ATEs compared to control, but not for VTEs. Based on our findings, patients with recent but controlled VTEs should not be denied the anti-VEGF treatment, and clinicians should pay more attention to the risk of high-grade ATEs associated with these drugs and must provide rigorous continuous monitoring.

Disclosure

The authors report no conflicts of interest in this work.

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