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RESEARCH ARTICLE

Hemorrhagic events in cancer patients treated with aflibercept: a meta-analysis

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Abstract Aflibercept (Ziv-aflibercept, VEGF Trap, AVE005) is an engineered protein that functions as a decoy receptor to bind vascular endothelial growth factor A (VEGF-A). Hemorrhagic events, including epistaxis, gastrointestinal bleeding, and pulmonary bleeding, is one of its major adverse effects, but the incidence rate and overall risk has not been systematically studied. Therefore, we conducted a meta-analysis of published clinical trials to investigate the incidence and relative risk of hemorrhagic events in cancer patients treated with aflibercept. Electronic databases including PubMed, Embase, Cochrane databases, and American Society of Clinical Oncology abstracts were searched. Eligible studies were phase II and III prospective clinical trials of cancer patients treated with aflibercept with toxicity profile on hemorrhagic events. Overall incidence rates, relative risk (RR), and 95 % confidence intervals (CI) were calculated using fixed or random effects models depending on the heterogeneity of the included studies. A total of 4,538 patients with a variety of solid tumors from 13 prospective clinical trials were included for the meta-analysis. The overall incidences of all-grade and high-grade hemorrhagic events in cancer patients were 22.1 % (95 % CI, 16.5–29.7 %) and 4.2 % (95 % CI, 3.9–4.6 %), respectively. The relative risks of hemorrhagic events of aflibercept compared to control were increased for all-grade (RR=2.63; 95 % CI, 2.07–3.34) and high-grade (RR=2.45, 95 % CI, 1.62–3.72) hemorrhagic events. The risk of developing high-grade hemorrhagic events with aflibercept was comparable to that of bevacizumab (RR=1.26; 95 % CI, 0.89–1.79). Aflibercept is associated with an increased risk of developing hemorrhagic events in patients with solid tumors. Close monitoring and management of hemorrhagic events are recommended.

Keywords Aflibercept · Hemorrhagic events · Meta-analysis

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Introduction

Angiogenesis is an important process in tumor growth, progression, and metastasis. Vascular endothelial growth factor (VEGF) is the main pro-angiogenic factor [1]. VEGF binds to both VEGFR-1 and VEGFR-2. The VEGF/VEGFR-2 pathway is thought to be the dominant promoter of angiogenesis [2]. VEGF signaling provides potential targets for antiangiogenic therapy in malignant tumors. Targeting VEGF by angiogenesis inhibitors have demonstrated clinical benefit in treating various solid tumors, including anti-VEGF antibody (bevacizumab), VEGF Trap (aflibercept), and VEGF tyrosine kinase inhibitors (sorafenib, sunitinib, vandetanib, pazopanib, axitinib, etc).

Aflibercept (Ziv-aflibercept, VEGF Trap, AVE005) is a recombinant fusion protein comprised of the extracellular domain from VEGFR-1 and VEGFR-2 fused with Fc region of human IgG1. It binds to VEGF-A, VEGF-B, and placental growth factor (PIGF), subsequently preventing ligand binding to VEGFR-1 and VEGFR-2. In vitro assays of aflibercept in human umbilical vein endothelial cells demonstrated the ability to completely block the phosphorylation of VEGFR-2 by VEGF-A, thereby blocking VEGF-A-induced cell

proliferation. The affinity of aflibercept for VEGF is superior to that of bevacizumab, and it is a more potent VEGF blocker than bevacizumab [3]. As a single agent, aflibercept led to decreases in tumor vessels and angiogenesis, tumor growth, and metastasis. Aflibercept also demonstrated synergy with other systemic treatments in a number of studies, leading to greater inhibition of tumor growth and change in tumor vasculature. Aflibercept is currently approved as second-line treatment for patients with metastatic colorectal cancer by US Food and Drug Administration.

VEGF inhibitors improve the clinical outcome of patients with solid tumors, but these agents have shown some adverse effects. The safety profile of aflibercept was similar to that of other angiogenesis inhibitors. Most events are of low grade, but some could be life-threatening. Hypertension, proteinuria, and thromboembolism are recognized as the hallmark class-related adverse effects associated with antiangiogenic therapy. Hemorrhagic events is also one of the most common adverse events of anti-VEGF agents [4]. Hemorrhage or bleeding events, including epistaxis, gastrointestinal bleeding and pulmonary hemorrhage, are found in some patients after aflibercept therapy. Epistaxis is the most common form of hemorrhage found with aflibercept. Due to the multiplicity of actions of VEGF on vascular walls, inhibition of VEGF signaling by anti-VEGF agents, such as aflibercept, predisposes vascular walls to hemorrhage. Vascular dysfunction is another area of concern with angiogenesis inhibitors such as aflibercept, as VEGF regulates vascular proliferation and permeability. The recognition and management of hemorrhagic events in cancer patients treated with aflibercept is an important issue since hemorrhagic events may cause severe outcomes. The incidence and relative risk of hemorrhagic events with aflibercept is unclear. Thus, we performed a meta-analysis of prospective clinical trials to determine the incidence and relative risk of hemorrhagic events among cancer patients treated with aflibercept.

Materials and methods

Search strategy

Several databases including PubMed, Embase, and Cochrane databases were searched for studies to include in the meta-analysis. Abstracts presented at the annual meetings of the American Society of Clinical Oncology (ASCO) was also searched manually. The upper date limit of March 2014 was applied, with no lower date limit. Searches include the following terms: ("aflibercept" or "VEGF-trap" or "AVE0005") and ("cancer" or "carcinoma" or "sarcoma"), and ("clinical trial" or "randomized controlled trial"). The references cited by the included studies were also used to complete the search.

Aflibercept is approved for the treatment of patients with previously treated colorectal cancer at a dose of 4 mg/kg every 2 weeks (Q2W). Therefore, clinical trials using aflibercept at the approved dosage were included. Clinical trials using aflibercept at doses of 6 mg/kg every 3 weeks (Q3W) were also included to assess the possible increased incidence of hemorrhagic events with these treatments.

Eligible criteria for inclusion in this meta-analysis are as follows: (1) prospective phase II and III clinical trials in cancer patients; (2) participants assigned to treatment with aflibercept at 4 mg/kg Q2W or 6 mg/kg Q3W; (3) the language was restricted in English; (4) data available regarding incidence or events of hemorrhagic events, including ecchymosis or petechiae, epistaxis, eye hemorrhage, gastrointestinal hemorrhage, gum hemorrhage, injection-site hemorrhage, hematemesis, hematuria, hemoptysis, nonspecific hemorrhage, hemothorax, melena, menorrhagia, metrorrhagia, purpura, rectal hemorrhage, retroperitoneal hemorrhage, CNS hemorrhage, and vaginal hemorrhage; and (5) if multiple publications of the same trial were retrieved, only the most recent publication was included. Phase I studies were excluded because of the different drug dosage and the relatively small number of patients on these trials. Abstracts of all candidate articles were read by two independent readers (LP and YZ). Articles that could not be categorized based on title and abstract alone were retrieved for full-text review. Disagreements were resolved by consensus between the two readers.

Study selection

Two investigators (LP and YZ) independently assessed the eligibility of the articles and abstracts identified by the search, and any discrepancy was resolved by consensus. Hemorrhagic events was extracted from the safety and toxicity profile in the primary studies. These clinical end points were all recorded according to versions 3.0 of the Common Terminology Criteria for Adverse Events (CTCAE) of National Cancer Institute (http://ctep.cancer.gov/reporting/ctc_archive.html). The CTC version 3.0 describes the grading of hemorrhagic events as follows: grade 1 indicating mild bleeding (intervention not indicated); grade 2 indicating symptomatic bleeding (medical intervention indicated); grade 3 indicating the need for transfusion, interventional radiology, or endoscopic or operative intervention (i.e., hemostasis of bleeding site); grade 4 indicating life-threatening consequences (major urgent intervention indicated); and grade 5 indicating death. We included all incidences of hemorrhagic events of grade 1 or above in our analysis.

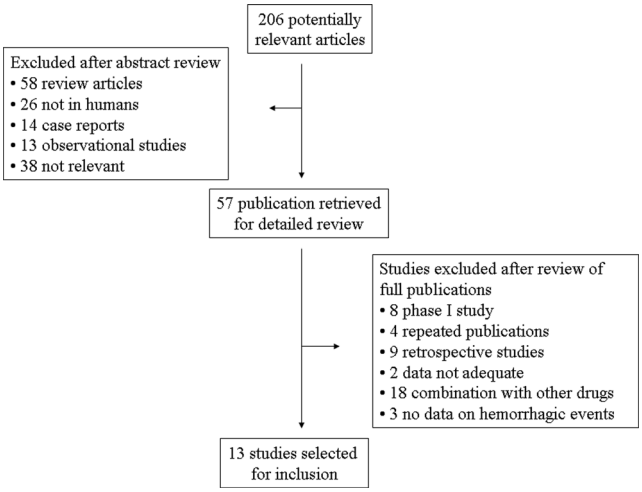

Fig. 1 Selection process for the trials included in the meta-analysis

Data analysis

Information was retrieved from the primary studies, using a standardized data collection form, including the following items: year of publication, first author, underlying malignancies, number of patients, treatment arm. If data from any of the above categories were not reported in the study, items were treated as "NR (not reported)." The data of the number of patients with all-grade and high-grade (≥grade 3) of hemorrhagic events and the number of patients receiving single-agent aflibercept were extracted from the toxicity profile. For each study, we derived the proportion and 95 % confidence interval (CI) of patients with hemorrhagic events. For studies with a control arm in the same trial, we also calculated and compared the relative risk (RR) of hemorrhagic events. For one study that reported zero events in the control arm, we applied the classic half-integer correction to calculate the RR and variance [5]. authors of the primary studies were not contacted for additional or unreported information. Between-study heterogeneity was estimated using the χ^2-based Q statistic [6]. Heterogeneity was considered statistically significant when $P<0.05$ or $I^2>50$ %. If heterogeneity existed, data were analyzed using a random effects model. In the absence of heterogeneity, a fixed effects model was used. To calculate the pooled incidence, an inverse variance statistical method was used. We also explored the differences in incidence of hemorrhagic events between aflibercept and bevacizumab. We used bevacizumab as the control (with RR=1.0) to calculate the RR of hypertension for aflibercept [7]. A statistical test with a P value less than 0.05 was considered significant. The presence of publication bias was evaluated by using the Begg's and Egger's tests [8, 9]. All of the

Table 1 Main characteristics and results of the eligible studies

Study	Year	Phase	Research	Underlying malignancy	Treatment arm	All-grade	High-grade	Patients
Tew [10]	2014	2	Parallel arm	Ovarian cancer	Aflibercept 4 mg/kg Q2W	15	0	109
					Aflibercept 2 mg/kg Q2W	4	0	106
Tannock [16]	2013	3	RCT	Prostate cancer	Aflibercept 6 mg/kg Q3W	270	26	611
					Placebo	90	6	598
Rougier [17]	2013	3	RCT	Pancreatic cancer	Aflibercept 4 mg/kg Q2W+gemcitabine	100	12	270
					Gemcitabine	25	4	271
Van Cutsem [12]	2012	3	RCT	mCRC	Aflibercept 4 mg/kg Q2W+FOLFIRI	231	18	611
					FOLFIRI	115	10	605
Tang [13]	2012	2	Single arm	mCRC	Aflibercept 4 mg/kg Q2W	18	1	74
Ramlau [14]	2012	3	RCT	NSCLC	Aflibercept 6 mg/kg Q3W+docetaxel	218	19	452
					Docetaxel	87	10	453
Mackay [18]	2012	2	Single arm	Sarcoma	Aflibercept 4 mg/kg Q2W	NS	1	62
Gotlieb [11]	2012	2	RCT	Ovarian cancer	Aflibercept 4 mg/kg Q2W	3	0	30
					Placebo	2	0	25
Coleman [19]	2012	2	Single arm	Endometrial cancer	Aflibercept 4 mg/kg Q2W	8	3	44
Tarhini [20]	2011	2	Single arm	Melanoma	Aflibercept 4 mg/kg Q2W	11	1	41
de Groot [21]	2011	2	Single arm	Glioma	Aflibercept 4 mg/kg Q2W	NS	1	58
Twardowski [22]	2010	2	Single arm	Urothelial cancer	Aflibercept 4 mg/kg Q2W	2	1	22
Leighl [15]	2010	2	Single arm	NSCLC	Aflibercept 4 mg/kg Q2W	34	3	96

Summary table of studies included in the meta-analysis

CI confidence interval, *RCT* randomized controlled trial, *NS* not specified

calculations were performed by STATA version 11.0 (Stata Corporation, College Station, TX).

Results

Study selection and characteristics

Our search yielded a total of 256 articles on aflibercept from the literature. After reviewing each publication, 13 original studies of full publication met our inclusion criteria, comprising 4,538 patients for final analysis. The selection process is summarized in Fig. 1. The major baseline characteristics of the 13 eligible studies were reported in Table 1, encompassing five randomized controlled trials (RCTs) and eight phase II clinical trials. Underlying malignancies include ovarian cancer (two trials) [10, 11], mCRC (colorectal cancer) (two trials) [12, 13], non-small cell lung cancer (two trials) [14, 15], prostate cancer (one trial) [16], pancreatic cancer (one trial) [17], sarcoma (one trial) [18], endometrial cancer

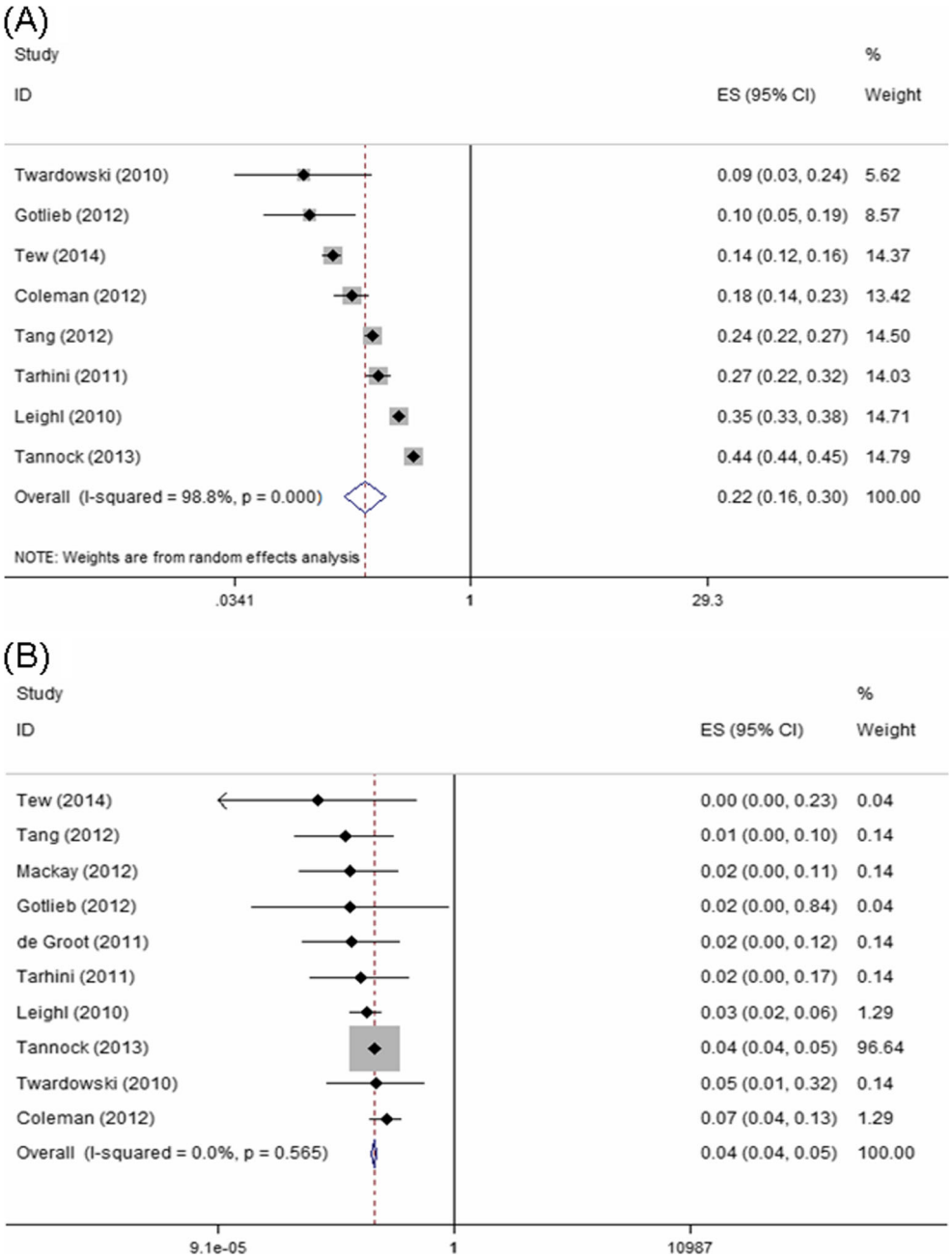

Fig. 2 Forest plot for meta-analysis of incidence relative risk of all-grade and high-grade hemorrhagic events in cancer patients treated with aflibercept. Each study was shown by the name of the lead author and year of publication. The summary incidence was also shown in the figure. Plots are arranged as follows: **a** incidence of all-grade hemorrhagic events; **b** incidence of high-grade hemorrhagic events

(one trial) [19], melanoma (one trial) [20], glioma (one trial) [21], and urothelial cancer (one trial) [22]. The sample size of the included studies ranged from 22 to 611 patients (median sample size, 106 patients). The studies were published between 2010 and 2014. For calculation of the RRs, five RCTs were pooled. We performed this meta-analysis in accordance with the guidelines of the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) statement [23].

Incidence of all-grade hemorrhagic events

The results of the meta-analysis were shown in Fig. 2. The incidence of all-grade hemorrhagic events ranged from 9.0 to 48.2 %; the lowest incidence was noted in a phase II single-arm trial among patients with urothelial cancer [22], and the highest incidence was observed in patients with NSCLC [14]. Our meta-analysis revealed a significant heterogeneity among included studies (I^2=98.8 %, P< 0.001), and the calculated summary incidence of all-grade hemorrhagic events among

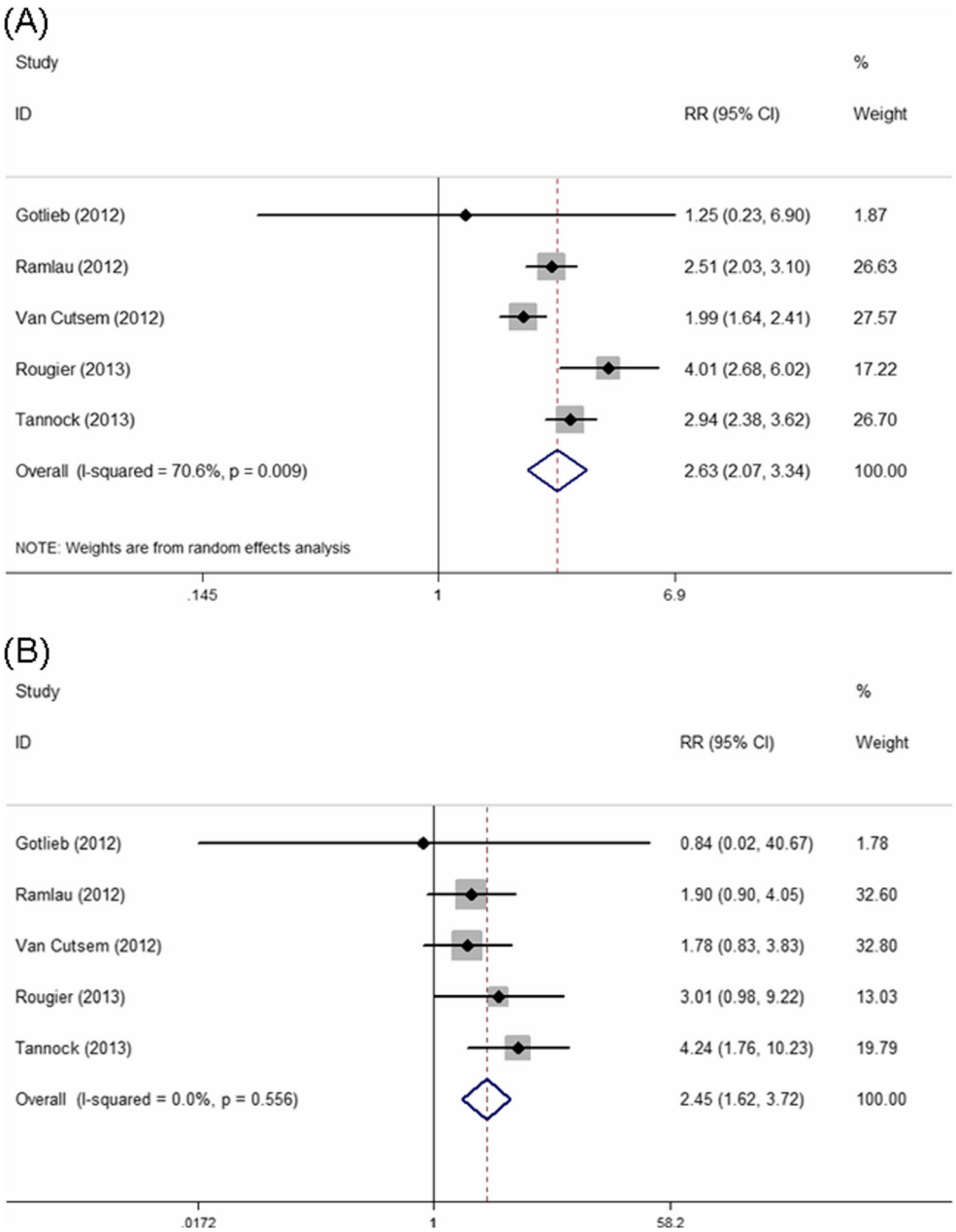

Fig. 3 Forest plot for meta-analysis of relative risk of all-grade and high-grade hemorrhagic events in cancer patients treated with aflibercept compared with control. Each study was shown by the name of the lead author and year of publication. Plots are arranged as follows: **a** relative risk of aflibercept-associated all-grade hemorrhagic events versus control; **b** relative risk of aflibercept-associated high-grade hemorrhagic events versus control

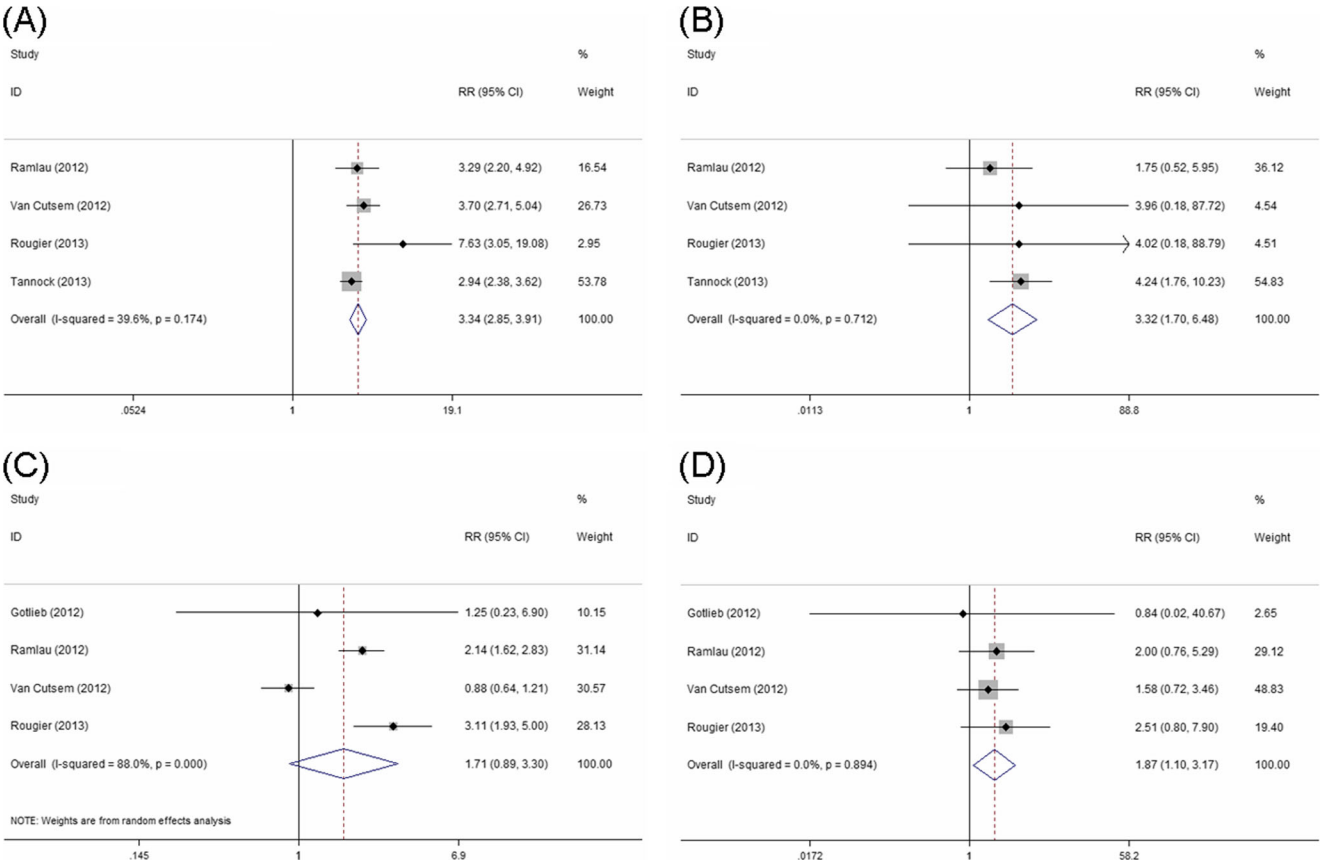

Fig. 4 Forest plot for meta-analysis of relative risk of specified and unspecified hemorrhagic events in cancer patients treated with aflibercept compared with control. Each study was shown by the name of the lead author and year of publication. Plots are arranged as follows: **a** relative risk of aflibercept-associated specified all-grade hemorrhagic events versus control; **b** relative risk of aflibercept-associated specified high-grade hemorrhagic events versus control; **c** relative risk of aflibercept-associated unspecified all-grade hemorrhagic events versus control; **d** relative risk of aflibercept-associated unspecified high-grade hemorrhagic events versus control

patients receiving aflibercept was 22.1 % (95 % CI, 16.5–29.7 %) using a random effects model (Fig. 2a).

Incidence of high-grade hemorrhagic events

The incidence of high-grade hemorrhagic events data ranges from 0 to 6.8 %. The highest incidence was observed in a phase II trial conducted by Coleman et al. in patients with endometrial cancer [19], and the lowest incidence was observed in patients with ovarian cancer [10]. The calculated summary incidence of high-grade hemorrhagic events among patients receiving aflibercept was 4.2 % (95 % CI, 3.9–4.6 %) using a fixed effects model (I^2= 0.0 %, P=0.565) (Fig. 2b).

Table 2 Incidence and risk of hemorrhagic events with angiogenesis inhibitors

Drugs	Incidence of hemorrhagic events (95 % CI)		Relative risk of hemorrhagic events (95 % CI)		References
	All-grade	High-grade	All-grade	High-grade	
Aflibercept	22.1 % (16.5–29.7)	4.2 % (3.9–4.6)	2.63 (2.07–3.34)	2.45 (1.62–3.72)	Present study
Bevacizumab	NR	2.8 % (2.1–3.8)	NR	1.60 (1.19–2.15)	[27]
Sorafenib	NR	NR	1.65 (1.22–2.22)	1.43 (0.75–2.74)	[28]
Sunitinib	NR	NR	3.35 (2.33–4.82)	1.68 (0.89–3.15)	[28]
Vandetanib	NR	NR	0.83 (0.65–1.06)	0.58 (0.28–1.21)	[28]
Axitinib	NR	NR	2.57 (1.12–5.89)	NR	[28]

CI confidence interval, *NR* not reported

Relative risk of hemorrhagic events

We then determined the RR of aflibercept-induced hemorrhagic events compared with control arm. For the calculation of relative risk, the included studies must involve the comparison of aflibercept against placebo, or the comparison of aflibercept with chemotherapy agent against placebo with the same chemotherapy agent. Altogether, five RCTs were pooled [16, 17, 12, 14, 11], comprising four phase 3 studies and one phase 2 study. The pooled RR showed that aflibercept treatment increased the risk of developing all-grade hemorrhagic events in cancer patients with a RR of 2.63 (95 % CI, 2.07–3.34; $P<0.001$, Fig. 3a) ($I^2=70.6$ %, $P=0.009$). The incidence for high-grade hemorrhagic events was significantly increased in cancer patients receiving aflibercept compared with control (RR=2.45; 95 % CI, 1.62–3.72, $P<0.001$, Fig. 3b) ($I^2=0.00$ %, $P=0.556$).

Risk of specified and unspecified hemorrhagic events

In comparison with controls, aflibercept was associated with a significantly increased risk of specified all-grade (RR, 3.34; 95 % CI, 2.85–3.91; $P<0.001$) and specified high-grade hemorrhagic events (RR=3.32; 95 % CI, 1.70–6.48; $P<0.001$). Additionally, a non-significantly increased risk of unspecified all-grade (RR=1.71; 95 % CI, 0.89–3.30; $P=0.106$) and a significantly increased risk of unspecified high-grade hemorrhagic events (RR=1.87; 95 % CI, 1.10–3.17; $P=0.021$) was observed (Fig. 4).

Difference in hemorrhagic events incidence between bevacizumab and aflibercept

In addition to aflibercept, other anti-angiogenesis drugs, such as bevacizumab, sorafenib, sunitinib, vandetanib, and axitinib, have been associated with the development of hemorrhagic events (Table 2). We explored the difference of high-grade incidence in hemorrhagic events induced by aflibercept in comparison of bevacizumab. The results showed that the risk of developing high-grade hemorrhagic events with aflibercept was comparable to that of bevacizumab (RR=1.26; 95 % CI, 0.89–1.79; $P=0.19$).

Publication bias

Begg's funnel plot and Egger's test were performed to evaluate the publication bias of the eligible studies. Ten and 13 studies investigating all-grade and high-grade hemorrhagic events induced by aflibercept yielded an Egger's test score of $P=0.001$ and $P=0.025$, respectively, indicating the presence of publication bias in the studies (Fig. 5).

Discussion

Angiogenesis is a crucial process in tissue development and growth. VEGF is the most potent and extensively studied. VEGF binding to VEGF receptors (VEGFR1, VEGFR2) initiates angiogenesis signaling process, including increased vascular permeability and endothelial cell proliferation [2]. Antiangiogenic drugs is postulated to block new blood vessel formation and lead to capillary regression [24]. VEGF inhibition is a validated anticancer strategy, and several agents have been designed to target VEGF and angiogenesis pathways.

Aflibercept (VEGF Trap, Ziv-aflibercept, or AVE005) is a recombinant protein consisting of domain 2 from VEGFR-1 fused to domain 3 from VEGFR-2, attached to the hinge

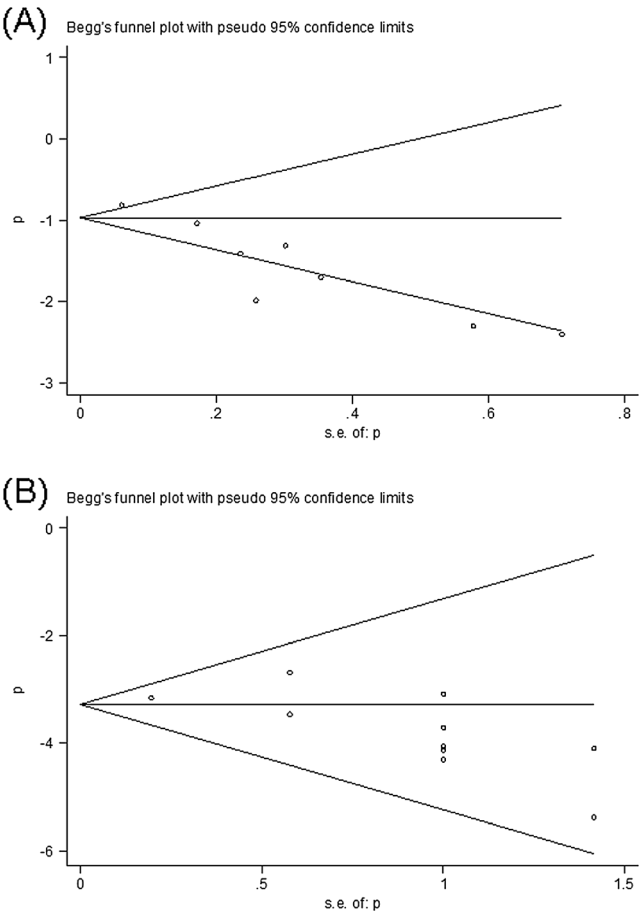

Fig. 5 Funnel plot for studies included in the meta-analysis. Plots are arranged as follows: **a** incidence of all-grade hemorrhagic events in cancer patients treated with aflibercept; **b** incidence of high-grade hemorrhagic events in cancer patients treated with aflibercept

region of the Fc domain of IgG1. In contrast to bevacizumab, aflibercept not only targets VEGF-A but also VEGF-B and PIGF, forming a pharmacologic blockade of the VEGF pathway. Aflibercept has a higher VEGF A binding affinity than bevacizumab [3]. It is approved by the Food and Drug Administration for use in combination with FOLFIRI regimen for second-line treatment of patients with metastatic colorectal cancer. Its application in other types of cancer is also undergoing extensive clinical assessment.

VEGF not only stimulates endothelial cell proliferation but also promotes endothelial cell survival and helps maintain vascular integrity. If VEGF is blocked, the repair capacity of endothelial cells are impaired and cause defects that expose pro-coagulant phospholipids on the luminal plasma membrane or underlying matrix, thus increasing the risk of hemorrhage [25]. Moreover, weakening of the wall of major vessels by tumor erosion, necrosis, cavitation, or other concurrent pathological conditions are likely to play a role in the occurrence of life-threatening hemorrhage [26]. Hemorrhagic events is one of the major side effects of aflibercept, and reported incidences vary substantially among clinical trials. The aim of this study is to gain a better understanding of the overall incidence and relative risk of hemorrhagic events in cancer patients treated with aflibercept. The present meta-analysis has combined 13 publications including five randomized controlled trials and eight phase II trials. Our meta-analysis results demonstrate that aflibercept is associated with an increased risk of developing hemorrhagic events. Our meta-analysis demonstrates that hemorrhagic events associated with aflibercept is mostly grades 1 and 2. Epistaxis was reported as the most frequent hemorrhagic event, and other events (GI hemorrhage, GU hemorrhage, hemoptysis, pulmonary hemorrhage, cerebral hemorrhage) were just cited as less frequent. In the incidence analysis, 1,027 patients were included for all-grade hemorrhagic events, and 1,147 were included for high-grade hemorrhagic events. The numerical difference was due to the fact that some trials reported only high-grade but not all-grade hemorrhagic events [18, 21]. The overall incidence of all-grade and high-grade hemorrhagic events was 22.1 % (95 % CI, 16.5–29.7 %) and 4.2 % (95 % CI, 3.9–4.6 %), respectively.

Our analysis data from randomized controlled trials showed a significant two-times risk of hemorrhagic events with aflibercept. The relative risks of hemorrhagic events of aflibercept compared to control were increased for all-grade (RR=2.63; 95 % CI, 2.07–3.34) and for high-grade (RR= 2.45; 95 % CI, 1.62–3.72) hemorrhagic events. Data were insufficient to analyze the differences of various underlying malignancies. As an exploratory analysis, we analyzed the risk of specified and unspecified hemorrhagic events with aflibercept. Results showed that the risk specified all-grade and high-grade hemorrhagic events were significantly increased with the use of aflibercept.

We also explore the difference in the incidence of hemorrhagic events associated with aflibercept compared with bevacizumab. The results show that the risk of developing high-grade hemorrhagic events with aflibercept is comparable to that of bevacizumab. We did not compare the incidence of all-grade hemorrhagic events between aflibercept and bevacizumab because the meta-analysis regarding hemorrhagic events in cancer patients treated with bevacizumab did not analyze all-grade hemorrhagic events [27]. As the development of aflibercept continues, this agent will come to head-to-head comparison with bevacizumab and VEGFR TKIs (sunitinib, sorafenib, pazopanib, cediranib, axitinib, and so on).

Hemorrhagic event is associated with aflibercept, which is highlighted by a black-box warning issued by the US Food and Drug Administration, recommending monitoring patients for signs and symptoms of GI bleeding and other severe bleeding For patients with high-grade hemorrhagic events, aflibercept should not be administered.

Our meta-analysis has several limitations. First, these studies are conducted at various institutions by different investigators and may have potential bias in reporting the types of adverse events. Secondly, our meta-analysis was based on data from trials that have published results in the literature, but not individual patient data. Thirdly, there was heterogeneity among the primary studies. It is possibly due to different design of the clinical trial and modes of treatment used in each study. In addition, our meta-analysis precludes a more comprehensive analysis such as adjusting for baseline factors and other differences that existed between the trials from which the data were pooled.

In summary, our meta-analysis is the first study to systematically estimate the incidence and relative risk of hemorrhagic events associated with aflibercept in cancer patients. The current analysis suggested that the use of aflibercept increased the risk of all-grade and high-grade hemorrhagic events. The relative risks of hemorrhagic events of aflibercept compared to control were increased for all-grade and high-grade hemorrhagic events. These results would provide important information for clinicians who use aflibercept to treat patients with solid tumors.

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Conflicts of interest None

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