

Risk of bleeding associated with antiangiogenic monoclonal antibodies bevacizumab and ramucirumab: a meta-analysis of 85 randomized controlled trials

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Aim: Bevacizumab and ramucirumab are antiangiogenic monoclonal antibodies, which target vascular endothelial growth factor-A and vascular endothelial growth factor receptor-2, respectively, used in various cancers. Bleeding events have been described with these two agents. We conducted an up-to-date meta-analysis to determine the relative risk (RR) associated with the use of antiangiogenic monoclonal antibodies, bevacizumab and ramucirumab.

Methods: This meta-analysis of randomized controlled trials was performed after searching PubMed, American Society for Clinical Oncology Abstracts, European Society for Medical Oncology Abstracts, and the proceedings of major conferences for relevant clinical trials. RR and 95% CIs were calculated by random-effects or fixed-effects models for all-grade and high-grade bleeding events related to the angiogenesis inhibitors.

Results: Eighty-five randomized controlled trials were selected for the meta-analysis, covering 46,630 patients. The results showed that antiangiogenic monoclonal antibodies significantly increased the risk of all-grade (RR: 2.38, 95% CI: 2.09–2.71, $p < 0.00001$) and high-grade (RR: 1.71, 95% CI: 1.48–1.97, $p < 0.00001$) bleeding compared with control arms. In the subgroup analysis, bevacizumab significantly increased the risk of all-grade (RR: 2.73, 95% CI: 2.24–3.33, $p < 0.00001$) and high-grade bleeding (RR: 1.98, 95% CI: 1.68–2.34, $p < 0.00001$), but ramucirumab only increased the risk of all-grade bleeding (RR: 1.94, 95% CI: 1.76–2.13, $p < 0.00001$) and no difference was observed for the risk of high-grade bleeding (RR: 1.04, 95% CI: 0.78–1.39, $p = 0.79$) compared with the control group. For lung cancer patients, bevacizumab significantly increased the risk of all-grade (RR: 4.72, 95% CI: 1.99–11.19, $p = 0.0004$) and high-grade pulmonary hemorrhage (RR: 3.97, 95% CI: 1.70–9.29, $p = 0.001$), but no significant differences in the risk of all-grade (RR: 1.09, 95% CI: 0.76–1.57, $p = 0.64$) and high-grade (RR: 1.22, 95% CI: 0.35–4.21, $p = 0.75$) pulmonary hemorrhage were observed for ramucirumab. The increased risk of all-grade and high-grade bleeding was also observed in colorectal cancer or non-colorectal tumors and low-dose or high-dose angiogenesis inhibitors.

Conclusion: Antiangiogenic monoclonal antibodies are associated with a significant increase in the risk of all-grade and high-grade bleeding. Ramucirumab may be different from bevacizumab in terms of the risk of high-grade bleeding and the risk of all-grade and high-grade pulmonary hemorrhage in lung cancer patients.

Keywords: bevacizumab, ramucirumab, antiangiogenic monoclonal antibodies, bleeding, meta-analysis

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Introduction

Angiogenesis is a complex biological process that plays an important role in sustaining growth, invasion, and the metastatic potential of tumors, and this process is mainly driven by vascular endothelial growth factor (VEGF).^{1,2} One of the VEGF family members, VEGF-A (commonly referred to as VEGF), has been demonstrated to be important in angiogenesis. Among all receptors, vascular endothelial growth factor receptor (VEGFR)-2 is widely thought to be principally linked to the stimuli of angiogenesis in malignancies. Blocking the function of VEGF-A or its receptor VEGFR-2 has been the most important antiangiogenic strategy for cancer therapy.³

Bevacizumab and ramucirumab are the most important antiangiogenic monoclonal antibodies, which target VEGF-A and its receptor VEGFR-2, respectively, used in various cancers. Bevacizumab is approved by the Food and Drug Administration (FDA) for the treatment of patients with metastatic colorectal cancer, advanced non-squamous non-small cell lung cancer (NSCLC), metastatic renal cell carcinoma, recurrent glioblastoma, advanced cervical cancer, and platinum-resistant ovarian cancer, and ramucirumab is approved by the FDA for the treatment of advanced gastric or gastroesophageal junction adenocarcinoma, metastatic NSCLC, and advanced colorectal cancer.

Bleeding events are a kind of major adverse events reported in clinical trials of bevacizumab and ramucirumab, which may cause severe outcomes that could be even life threatening.⁴ The main mechanism of bleeding is that angiogenesis inhibitors disrupt tumor vasculature through inhibition of VEGF signaling and lead to thrombosis or bleeding.^{1,5}

However, the relative risk (RR) of bleeding events in patients with cancer treated with these two antiangiogenic monoclonal antibodies has yet to be defined. Therefore, we conducted an up-to-date meta-analysis of available clinical trials to determine the RR of bleeding in cancer patients treated with antiangiogenic monoclonal antibodies, bevacizumab and ramucirumab.

Materials and methods

Search strategy

This study was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement⁶ (Supplementary material). We searched PubMed, American Society for Clinical Oncology Abstracts, and European Society for Medical Oncology Abstracts for relevant trials till September 2017. Moreover, we also searched the clinical trial registration website ([https://](https://www.ClinicalTrials.gov)

www.ClinicalTrials.gov) to obtain information on registered randomized controlled trials (RCTs). Keywords used in the search were “bevacizumab,” “avastin,” “ramucirumab,” “IMC1121B,” “LY3009806,” and “randomized controlled trials.” The search was limited to RCTs published in English.

Selection of trials

Data abstraction and quality assessment were conducted independently by two reviewers. Disagreements were resolved by discussion with an independent expert. The RCTs were eligible for inclusion in our meta-analysis: 1) prospective Phase II and Phase III RCTs in patients with cancer, 2) random assignment of participants to these two antiangiogenic monoclonal antibodies treatment or control groups, 3) available data, including the event or incidence of bleeding and sample size for analysis. Phase I and single-arm phase II trials were excluded because of their lack of control groups.

Data extraction

We extracted details on study characteristics, treatment information, results, and safety profiles from the selected trials. Clinical endpoints were obtained from the safety profile of each clinical trial. All-grade, high-grade bleeding and all-grade, high-grade pulmonary hemorrhage in lung cancers were recorded according to the version of National Cancer Institute-Common Terminology Criteria for Adverse Events used in each trial.

Statistical analysis

Data were calculated by Review Manager version 5.2 (The Nordic Cochrane Centre, Copenhagen, Denmark). For the outcomes, the RR was calculated for dichotomous data. Statistical heterogeneity in the results of the trials was assessed by the chi-square test, and expressed by the I^2 index.⁷ When there was no statistically significant heterogeneity, a pooled effect was calculated with a fixed-effect model. When considerable heterogeneity was found ($p < 0.1$, or $I^2 > 50\%$), a random-effect model was employed. Subgroup analysis was conducted to examine whether the RRs of all-grade and high-grade bleeding varied by drug type, drug dosage, and cancer type.

Results

Search results

We reviewed 2,045 potentially relevant articles from our initial search strategies. A total of 1,906 articles were excluded on screening abstracts and titles for the following reasons: review articles, case reports, basic researches,

Phase I or single-arm Phase II studies, irrelevant topics, and duplicate reports. The remaining 139 articles were retrieved for full evaluation, and 54 articles were excluded for unavailable data for assessment of bleeding or antiangiogenic monoclonal antibodies in both treatment and control arms. Finally, 85 RCTs were included in this meta-analysis.^{8–92} The study search process is shown in a flow chart (Figure 1).

Patients

A total of 85 studies and 46,630 patients were included for the analysis. Bevacizumab was investigated in 72 trials^{8–79} and ramucirumab was investigated in 13 trials.^{80–92} All of the studies included 21 colorectal cancer,^{8–26,85,86} 15 breast cancer,^{27–39,87,88} 16 lung cancer,^{40–52,80–82} three renal cell cancer,^{53,54} two pancreatic cancer,^{55,56} five ovarian cancer,^{57–61} six gastric or gastroesophageal junction adenocarcinoma,^{62–65, 89–91} three glioblastoma,^{66–68} one lymphoma,⁶⁹ one lymphocytic leukemia,⁷⁰ two melanoma,^{71,72} two malignant mesothelioma,^{73,74} one prostate cancer,⁷⁵ one cervical cancer,⁷⁶ one leiomyosarcoma,⁷⁷ two urothelial carcinoma,^{83,84} two hepatocellular carcinoma,^{78,92} and one soft tissue sarcoma.⁷⁹ In addition, 35 trials^{9,10,12–20,22–26,46,49,52,55,58,62–65,72,78–84,87,88} were treated with low-dose drugs (28 trials for bevacizumab at 2.5 mg/kg/week, seven trials for ramucirumab at 3.3 mg/kg/week) and 46 trials^{11,21,27,28,30–39,41,42,44,45,47,48,50,51,53,54,56,57,59–61,66–71, 73–77,85,86,89–92} were treated with high-dose drugs (40 trials for bevacizumab at 5 mg/kg/week, six trials for ramucirumab at 4 mg/kg/week). Other 4 three-arm trials^{8,29,40,43} were two

arms of different dosage levels of bevacizumab and one arm of control. All of these RCTs were judged to be of adequate quality (Jadad score is 3–5). Baseline characteristics of the 85 RCTs are provided in Table 1.

RR of all-grade bleeding

Forty-three RCTs were available to calculate the RR of all-grade bleeding in patients assigned to angiogenesis inhibitors arms versus control arms. The results showed that antiangiogenic monoclonal antibodies significantly increased the risk of all-grade (RR: 2.38, 95% CI: 2.09–2.71, $p < 0.00001$) bleeding compared with control arms. There was statistically significant heterogeneity ($I^2 = 74\%$) across the trials; we incorporated it into a random-effects model (Figure 2).

RR of high-grade bleeding

The RR of high-grade (\geq grade 3) bleeding was determined in 82 RCTs. The results showed that antiangiogenic monoclonal antibodies significantly increased the risk of all-grade bleeding (RR: 1.71, 95% CI: 1.48–1.97, $p < 0.00001$) with a fixed-effects models ($I^2 = 19\%$) (Figure 3).

RR according to drug type

As an exploratory analysis, patients were stratified according to drug type. We found that bevacizumab significantly increased the risk of all-grade (RR: 2.73, 95% CI: 2.24–3.33, $p < 0.00001$) and high-grade bleeding (RR: 1.98, 95% CI: 1.68–2.34, $p < 0.00001$), but ramucirumab only increased

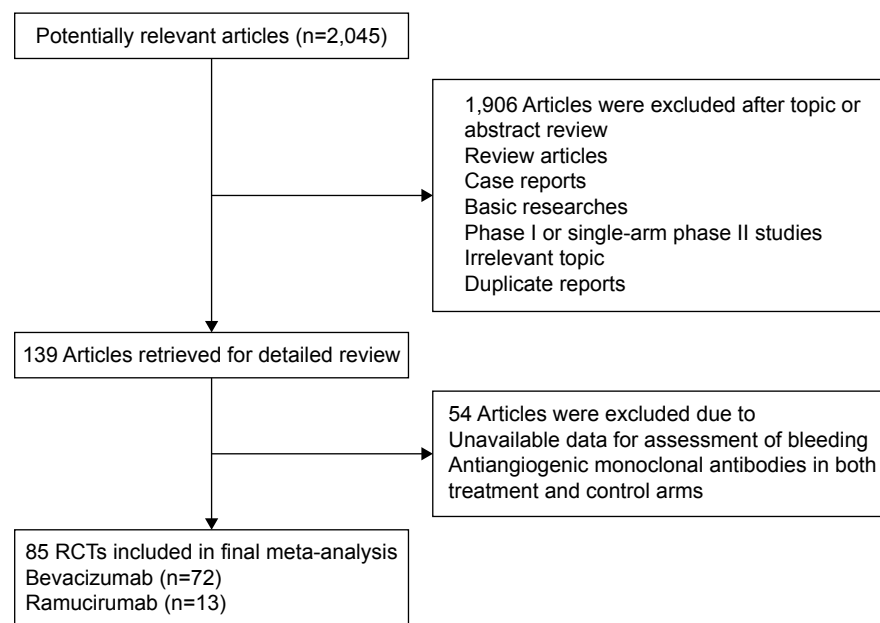


Figure 1 Outline of the search flow diagram.

Abbreviation: RCTs, randomized controlled trials.

Table 1 Characteristics of studies included in the meta-analysis

Author	Year	Malignancy	Phase	No. in intervention/control	Concurrent treatment	Dose (mg/kg/week)	No. of bleeding events in intervention/control	
							All grade	Grade ≥ 3
Bevacizumab								
Kabbinavar et al ⁸	2003	CRC	II	67/35	Fluorouracil + leucovorin	2.5 or 5	NR	3/0
Hurwitz et al ⁹	2004	CRC	III	393/397	Irinotecan + fluorouracil + leucovorin	2.5	NR	12/10
Kabbinavar et al ¹⁰	2005	CRC	II	100/104	Fluorouracil + leucovorin	2.5	NR	5/3
Giantonio et al ¹¹	2007	CRC	III	287/285	Oxaliplatin + fluorouracil + leucovorin	5	NR	10/1
Saltz et al ¹²	2008	CRC	III	694/675	Capecitabine + oxaliplatin/fluorouracil + folinic acid + oxaliplatin	2.5	NR	13/8
Allegra et al ¹³	2009	CRC	III	1,326/1,321	Oxaliplatin + fluorouracil + leucovorin	2.5	NR	25/25
Tebbutt et al ¹⁴	2010	CRC	III	157/156	Capecitabine	2.5	19/19	2/4
Statopoulos et al ¹⁵	2010	CRC	III	114/108	Irinotecan + fluorouracil + leucovorin	2.5	3/0	NR
Guan et al ¹⁶	2011	CRC	III	141/70	Irinotecan + fluorouracil + leucovorin	2.5	NR	1/1
Dotan et al ¹⁷	2012	CRC	II	12/11	Capecitabine + oxaliplatin + cetuximab	2.5	6/4	0/0
De Gramont et al ¹⁸	2012	CRC	III	1,145/1,126	Oxaliplatin + fluorouracil + leucovorin	2.5	NR	14/6
Bennouna et al ¹⁹	2013	CRC	III	401/409	Fluorouracil/capecitabine + oxaliplatin/irinotecan	2.5	NR	8/1
Cunningham et al ²⁰	2013	CRC	III	134/136	Capecitabine	2.5	34/9	0/1
Cao et al ²¹	2015	CRC	II	65/77	Irinotecan + fluorouracil + leucovorin	5	NR	5/0
Hegewisch-Becker et al ²²	2015	CRC	III	156/158	None	2.5	14/11	0/1
Passardi et al ²³	2015	CRC	III	176/194	Irinotecan + fluorouracil + leucovorin/oxaliplatin + fluorouracil + leucovorin	2.5	30/9	NR
Masi et al ²⁴	2015	CRC	III	91/92	Irinotecan + fluorouracil + leucovorin/oxaliplatin + fluorouracil + leucovorin	2.5	19/2	0/0
Koeberle et al ²⁵	2015	CRC	III	131/131	None	2.5	5/1	0/0
Snoeren et al ²⁶	2017	CRC	III	39/36	Capecitabine + oxaliplatin	2.5	NR	0/1
Miller et al ²⁷	2005	BC	III	229/215	Capecitabine	5	66/24	1/1
Miller et al ²⁸	2007	BC	III	365/346	Paclitaxel	5	NR	2/0
Miles et al ²⁹	2010	BC	III	499/231	Docetaxel	2.5 or 5	NR	5/2
Brufsky et al ³⁰	2011	BC	III	458/221	Capecitabine/taxane/gemcitabine/vinorelbine	5	NR	8/0
Robert et al ³¹	2011	BC	III	817/403	Capecitabine/taxane/anthracycline	5	NR	14/1
von Minckwitz et al ³²	2012	BC	III	956/969	Epirubicin/cyclophosphamide/docetaxel	5	NR	4/3
Gianni et al ³³	2013	BC	III	215/206	Docetaxel + trastuzumab	5	NR	3/1
Cameron et al ³⁴	2013	BC	III	1,288/1,271	Anthracycline/taxane	5	NR	8/2
Coudert et al ³⁵	2014	BC	II	47/25	Trastuzumab + docetaxel	5	NR	0/0
von Minckwitz et al ³⁶	2014	BC	III	245/238	Taxane/anthracycline/capecitabine/vinorelbine/gemcitabine/cyclophosphamide	5	33/18	1/4
Sikov et al ³⁷	2015	BC	II	215/218	Paclitaxel \pm carboplatin–doxorubicin + cyclophosphamide	5	NR	7/0
Diéras et al ³⁸	2015	BC	II	56/57	Trebananib + paclitaxel	5	29/17	0/0
Miles et al ³⁹	2017	BC	III	238/233	Paclitaxel	5	106/62	2/2
Johnson et al ⁴⁰	2004	LC	II	66/32	Carboplatin + paclitaxel	2.5 or 5	NR	6/0

Sandler et al ⁴¹	2006	LC	III	427/440	Paclitaxel + carboplatin	5	NR	19/3
Herbst et al ⁴²	2007	LC	II	39/42	Docetaxel/pemetrexed	5	NR	3/1
Reck et al ⁴³	2009	LC	III	659/327	Cisplatin + gemcitabine	2.5 or 5	NR	28/6
Herbst et al ⁴⁴	2011	LC	III	313/313	Erlotinib	5	NR	10/7
Niho et al ⁴⁵	2012	LC	II	119/58	Carboplatin + paclitaxel	5	94/18	2/0
Boutsikou et al ⁴⁶	2013	LC	III	116/113	Docetaxel + carboplatin ± erlotinib	2.5	7/0	3/0
Seto et al ⁴⁷	2014	LC	II	75/77	Erlotinib	5	54/22	2/0
Zhou et al ⁴⁸	2015	LC	III	140/134	Carboplatin, paclitaxel	5	NR	2/1
Pujol et al ⁴⁹	2015	LC	II-III	37/37	Cisplatin + etoposide ± epidoxorubicin + cyclophosphamide	2.5	7/2	0/0
Takeda et al ⁵⁰	2016	LC	II	50/50	Docetaxel	5	20/3	0/0
Karayama et al ⁵¹	2016	LC	II	45/35	Pemetrexed	5	NR	0/0
Tiseo et al ⁵²	2017	LC	III	95/103	Cisplatin + etoposide	2.5	NR	0/0
Escudier et al ⁵³	2007	RCC	III	337/304	Interferon α	5	112/28	11/1
Rini et al ⁵⁴	2010	RCC	III	362/347	Interferon α	5	21/4	4/1
Van Cutsem et al ⁵⁵	2009	PC	III	296/287	Gemcitabine + erlotinib	2.5	124/67	22/16
Kindler et al ⁵⁶	2010	PC	III	277/263	Gemcitabine	5	NR	5/4
Burger et al ⁵⁷	2011	OC	III	608/601	Paclitaxel + carboplatin	5	NR	14/5
Perren et al ⁵⁸	2011	OC	III	745/753	Paclitaxel + carboplatin	2.5	295/87	9/2
Pujade-Lauraine et al ⁵⁹	2014	OC	III	179/181	PLD/paclitaxel/topotecan	5	NR	2/2
Aghajanian et al ⁶⁰	2015	OC	III	247/233	Gemcitabine + carboplatin	5	170/78	15/2
Coleman et al ⁶¹	2017	OC	III	330/327	Paclitaxel + carboplatin	5	140/27	6/3
Ohtsu et al ⁶²	2011	GC	III	386/381	Cisplatin + capecitabine	2.5	NR	9/9
Okines et al ⁶³	2013	GC	II/III	99/101	Epirubicin + cisplatin + capecitabine	2.5	NR	1/3
Shen et al ⁶⁴	2015	GC, GEJC	III	100/101	Capecitabine + cisplatin	2.5	NR	12/4
Cunningham et al ⁶⁵	2017	GEJC	II/III	468/477	Epirubicin + cisplatin + capecitabine	2.5	15/7	2/2
Chinot et al ⁶⁶	2014	Glioblastoma	III	461/450	Radiotherapy + temozolomide	5	186/97	15/8
Gilbert et al ⁶⁷	2014	Glioblastoma	III	260/233	None	5	NR	4/2
Balana et al ⁶⁸	2016	Glioblastoma	II	48/45	Temozolomide	5	NR	5/0
Seymour et al ⁶⁹	2014	Lymphoma	III	395/386	Rituximab + doxorubicin + vincristine + cyclophosphamide + prednisone instead of R-CHOP	5	77/31	8/1
Kay et al ⁷⁰	2016	Lymphocytic leukemia	II	33/32	Pentostatin + cyclophosphamide + rituximab	5	NR	1/0
Kim et al ⁷¹	2012	Melanoma	II	143/69	Paclitaxel + carboplatin	5	NR	2/5
Corrie et al ⁷²	2014	Melanoma	III	671/672	None	2.5	153/13	1/1
Kindler et al ⁷³	2012	MM	II	53/55	Gemcitabine + cisplatin	5	NR	4/1
Zalcman et al ⁷⁴	2016	MM	III	222/224	Pemetrexed + cisplatin	5	91/16	2/0
Kelly et al ⁷⁵	2012	Prostate cancer	III	504/505	Docetaxel + prednisone	5	NR	35/16
Tewari et al ⁷⁶	2014	Cervical cancer	III	220/219	Paclitaxel/topotecan + cisplatin	5	NR	10/2
Hensley et al ⁷⁷	2015	uLMS	III	52/51	Gemcitabine + docetaxel	5	1/2	0/1
Pinter et al ⁷⁸	2015	HC	II	16/11	TACE	2.5	3/1	3/1
Chisholm et al ⁷⁹	2017	STTs	II	71/79	Ifosfamide + vincristine + actinomycin-D + doxorubicin instead of VADO/IVA/cyclophosphamide + vinorelbine	2.5	NR	2/6

(Continued)

Table 1 (Continued)

Author	Year	Malignancy	Phase	No. in intervention/control	Concurrent treatment	Dose (mg/kg/week)	No. of bleeding events in intervention/control	
							All grade	Grade ≥ 3
Ramucirumab								
Yoh et al ⁸⁰	2016	LC	II	76/81	Docetaxel	3.3	39/23	2/0
Doebele et al ⁸¹	2015	LC	II	67/69	Pemetrexed + cisplatin	3.3	26/13	2/1
Garon et al ⁸²	2014	LC	III	627/618	Docetaxel	3.3	181/94	15/14
Petrylak et al ⁸³	2016	UC	II	46/45	Docetaxel	3.3	31/12	2/1
Petrylak et al ⁸⁴	2017	UC	III	263/267	Docetaxel	3.3	67/46	8/12
Taberno et al ⁸⁵	2015	CRC	III	529/528	None	4	232/120	13/9
Moore et al ⁸⁶	2016	CRC	II	52/49	Oxaliplatin + fluorouracil + leucovorin	4	25/9	NR
Mackey et al ⁸⁷	2015	BC	III	752/382	Docetaxel	3.3	361/85	7/7
Yardley et al ⁸⁸	2016	BC	II	69/65	Eribulin	3.3	13/3	1/1
Fuchs et al ⁸⁹	2014	GC or GEJC	III	236/115	None	4	30/13	8/3
Wilke et al ⁹⁰	2014	GC or GEJC	III	327/329	Paclitaxel	4	137/59	14/8
Yoon et al ⁹¹	2016	GC, EC, or GEJC	II	82/80	Oxaliplatin + fluorouracil + leucovorin	4	36/20	5/5
Zhu et al ⁹²	2015	HC	III	277/276	None	4	90/55	17/21

Abbreviations: CRC, colorectal cancer; BC, breast cancer; LC, lung cancer; RCC, renal cell carcinoma; PC, pancreatic cancer; OC, ovarian cancer; GC, gastric cancer; MM, malignant mesothelioma; uLMS, uterine leiomyosarcoma; UC, urothelial carcinoma; EC, esophagus cancer; GEJC, gastroesophageal junction cancer; HC, hepatocellular carcinoma; STSs, soft tissue sarcomas; NR, not reached; TACE, transarterial chemoembolization.

the risk of all-grade bleeding (RR: 1.94, 95% CI: 1.76–2.13, $p < 0.00001$) and no difference was observed for the risk of high-grade bleeding (RR: 1.04, 95% CI: 0.78–1.39, $p = 0.79$) compared with the control group. RR of all-grade and high-grade bleeding according to drug type is summarized in Tables 2 and 3, respectively.

In addition, we further assessed the risk of pulmonary hemorrhage of bevacizumab and ramucirumab in all lung cancer patients. The results showed that bevacizumab significantly increased the risk of all-grade (RR: 4.72, 95% CI: 1.99–11.19, $p = 0.0004$) and high-grade pulmonary hemorrhage (RR: 3.97, 95% CI: 1.70–9.29, $p = 0.001$), but no significant differences in the risk of all-grade (RR: 1.09, 95% CI: 0.76–1.57, $p = 0.64$) and high-grade (RR: 1.22, 95% CI: 0.35–4.21, $p = 0.75$) pulmonary hemorrhage were observed for ramucirumab. RR of all-grade and high-grade pulmonary hemorrhage is shown in Figures 4 and 5, respectively.

RR according to drug dosage

In the subgroup analysis by dosage, the increased risk of all-grade and high-grade bleeding was observed in both low-dose and high-dose angiogenesis inhibitors.

The risks of all-grade bleeding were comparable between patients with low-dose angiogenesis inhibitors (RR: 2.46, 95% CI: 1.95–3.11) and high-dose angiogenesis inhibitors (RR: 2.34, 95% CI: 2.00–2.73) (Table 2). The risk of high-grade bleeding was more frequently observed in patients with high-dose angiogenesis inhibitors (RR: 2.17, 95% CI: 1.79–2.64) than in those with low-dose angiogenesis inhibitors (RR: 1.31, 95% CI: 1.06–1.60) (Table 3).

RR according to tumor type

Studies were further stratified according to tumor type (colorectal cancer vs non-colorectal tumors). Increased risk of all-grade and high-grade bleeding was observed in both the colorectal cancer arm and non-colorectal tumors arm. The risks of all-grade (RRs for colorectal cancer and non-colorectal tumors were 2.24, 95% CI: 1.58–3.19 and 2.42, 95% CI: 2.09–2.80, respectively) (Table 2) and high-grade bleeding (RRs for colorectal cancer and non-colorectal tumors were 1.52, 95% CI: 1.13–2.03 and 1.77, 95% CI: 1.50–2.09, respectively) (Table 3) were comparable between patients with colorectal cancer and non-colorectal tumors.

Publication bias

To minimize publication bias, we selected papers strictly according to the inclusion criteria. Furthermore, a funnel plot

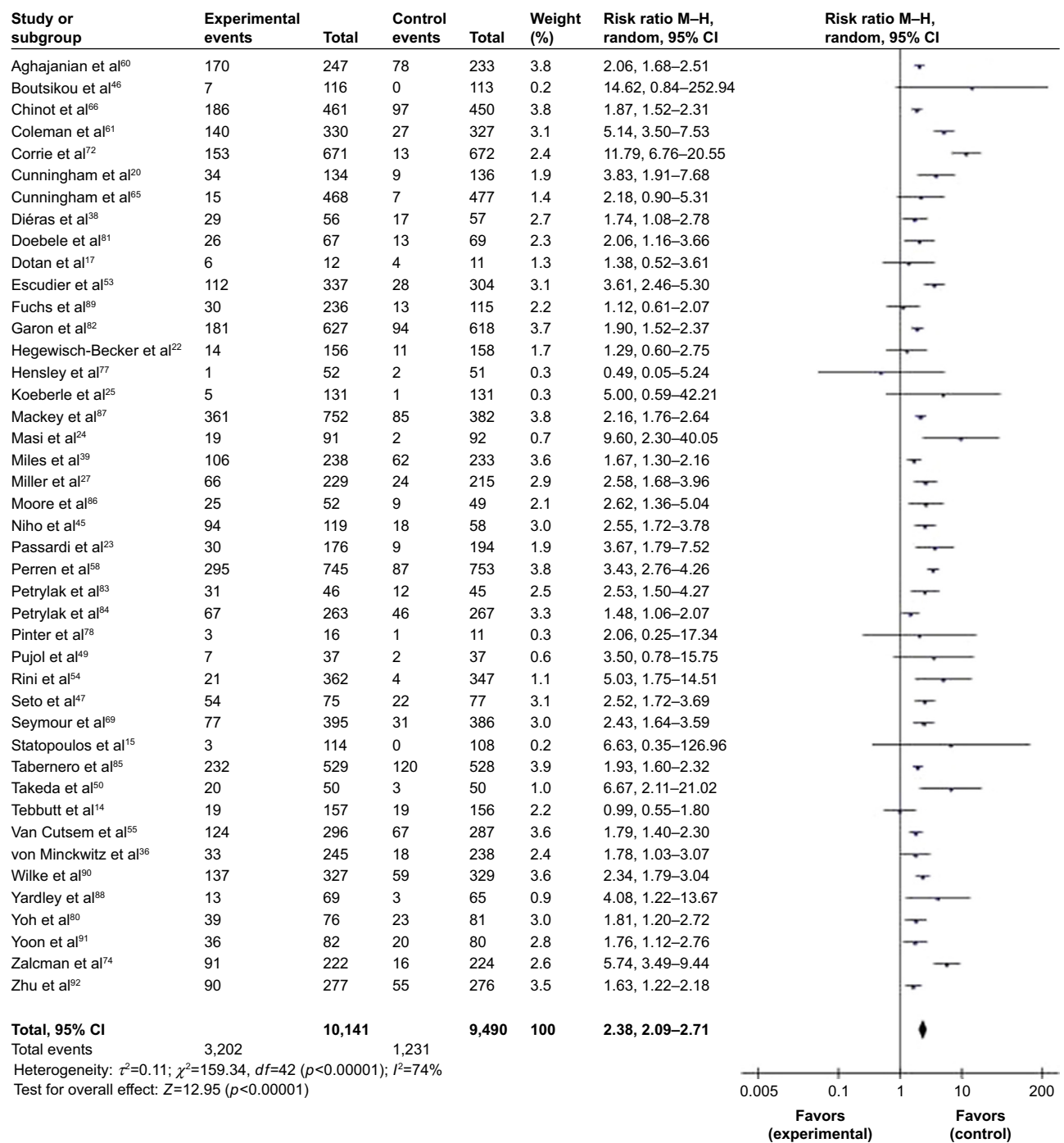


Figure 2 RR of all-grade bleeding.
Abbreviations: M-H, Mantel-Haenszel; RR, relative risk.

was used to detect publication bias and no apparent bias was found according to it for all-grade and high-grade bleeding.

Discussion

To the best of our knowledge, this is the first and the largest meta-analysis to assess the risk of bleeding associated with antiangiogenic monoclonal antibodies bevacizumab and

ramucirumab. The results of our meta-analysis showed a significant 2.38-fold increased all-grade bleeding risk and a 1.71-fold increased high-grade bleeding risk with these agents. A similar risk of bleeding is also associated with other VEGF receptor tyrosine kinase inhibitors.⁹³

In order to identify potential risk factors, we performed subgroup analysis according to drug types. The results

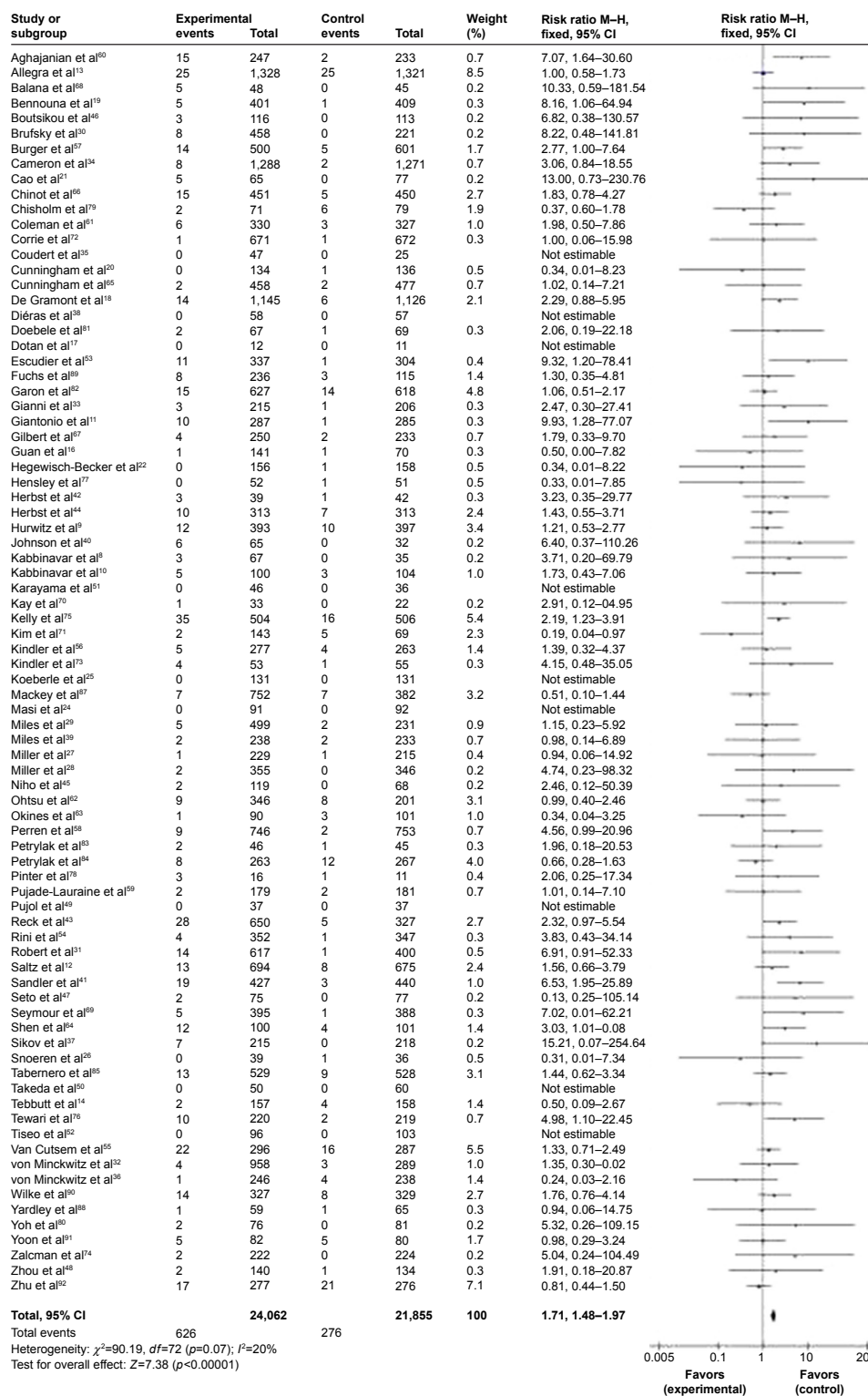


Figure 3 RR of high-grade bleeding.

Abbreviations: M-H, Mantel-Haenszel; RR, relative risk.

showed that ramucirumab differed from bevacizumab in terms of the risk of high-grade bleeding and the risk of all-grade and high-grade pulmonary hemorrhage in lung cancer patients. The mechanisms underlying these

differences remained unclear. A possible explanation was that bevacizumab, as an anti-VEGF-A agent, specified both VEGFR-1 and VEGFR-2, whereas ramucirumab was only specified for VEGFR-2. VEGFR-2 was the major mediator

Table 2 RR of all-grade bleeding associated with angiogenesis inhibitors in the subgroup analysis

Bleeding	No. of trials	No. of events/total (%)		RR, 95% CI
		Treatment	Control	
Type of drug				
Bevacizumab	30	1,934/6,738 (28.7)	679/6,586 (10.3)	2.73, 2.24–3.33
Ramucirumab	13	1,268/3,403 (37.3)	552/2,904 (19.0)	1.94, 1.76–2.13
Drug dosage				
Low dose	22	1,452/5,220 (27.8)	508/4,863 (10.4)	2.46, 1.95–3.11
High dose	21	1,750/4,921 (35.6)	723/4,627 (15.6)	2.34, 2.00–2.73
Tumor types				
Colorectal cancer	10	387/1,552 (24.9)	184/1,563 (11.8)	2.24, 1.58–3.19
Non-colorectal cancer	33	2,815/8,589 (32.8)	1,047/7,927 (13.2)	2.42, 2.09–2.80

Abbreviation: RR, relative risk.

of VEGF-driven responses in endothelial cells. The precise function of VEGFR-1 was not entirely established and some studies showed that VEGFR-1 could also regulate proliferation and survival of endothelial cells.^{94–97} Increased level of tumor VEGFR-1 expression has been shown to be associated with high tumor angiogenesis.⁹⁶ VEGF/VEGFR-1 signaling-mediated tumor cell monocyte chemoattractant protein-1 expression could represent a mechanism responsible for the tumor angiogenic switch.⁹⁷ Therefore, bevacizumab increased the risk of bleeding by inhibiting both VEGFR-1 and VEGFR-2. Squamous cell tumors are more frequently centrally located and have a greater tendency to cavitate as compared to adenocarcinoma, which is the main risk factor of pulmonary hemorrhage.⁹⁸ The difference in the risk of pulmonary hemorrhage caused bevacizumab to be used only for non-squamous NSCLC and ramucirumab to be used for any tumor histology of NSCLC.

Our study also demonstrated that both low-dose and high-dose angiogenesis inhibitors increased the risk of bleeding. The risk of high-grade bleeding was more frequently observed in patients with high-dose angiogenesis inhibitors, suggesting that the risk may be dose-dependent and close

supervision and careful management should be emphasized especially in patients with high dosage.

In a meta-analysis of bevacizumab, patients with colorectal cancer were found to have the highest risk of bleeding compared to other tumors.⁹⁹ For colorectal cancer patients, high-grade bleeding such as perforation was commonly fatal and life threatening.¹⁰⁰ Therefore, we performed a subgroup analysis according to colorectal cancer and non-colorectal tumors in order to identify the potential risk factors. Results showed that the risk of all-grade and high-grade bleeding was comparable between patients with colorectal cancer and non-colorectal tumors, suggesting that the increased risk of bleeding is associated with many tumor types.

Limitations

There are several limitations in this meta-analysis. First, we performed stratification analysis only for colorectal cancer and non-colorectal tumor types because too many tumor types were included in the analysis and assessment was difficult. Second, we did not evaluate the risk of pulmonary hemorrhage between bevacizumab and ramucirumab in

Table 3 RR of high-grade bleeding associated with angiogenesis inhibitors in the subgroup analysis

Bleeding	No. of trials	No. of events/total (%)		RR, 95% CI
		Treatment	Control	
Type of drug				
Bevacizumab	70	432/20,731 (2.1)	194/19,000 (1.0)	1.98, 1.68–2.34
Ramucirumab	12	94/3,351 (2.8)	82/2,855 (2.9)	1.04, 0.78–1.39
Drug dosage				
Low dose	37	203/10,569 (1.9)	149/10,089 (1.5)	1.31, 1.06–1.60
High dose	49	323/13,513 (2.4)	135/12,391 (1.1)	2.17, 1.79–2.64
Tumor types				
Colorectal cancer	18	111/5,868 (1.9)	71/5,747 (1.2)	1.52, 1.13–2.03
Non-colorectal cancer	64	415/18,214 (2.3)	205/16,108 (1.3)	1.77, 1.50–2.09

Abbreviation: RR, relative risk.

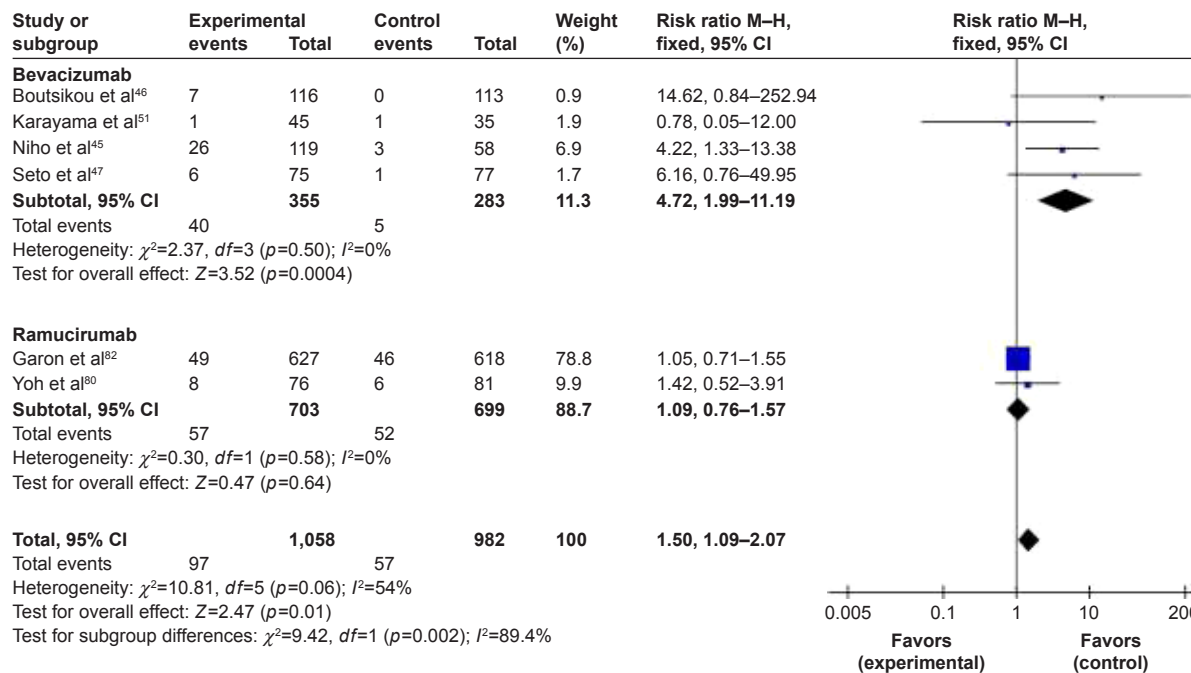


Figure 4 RR of all-grade pulmonary hemorrhage. Abbreviations: M-H, Mantel-Haenszel; RR, relative risk.

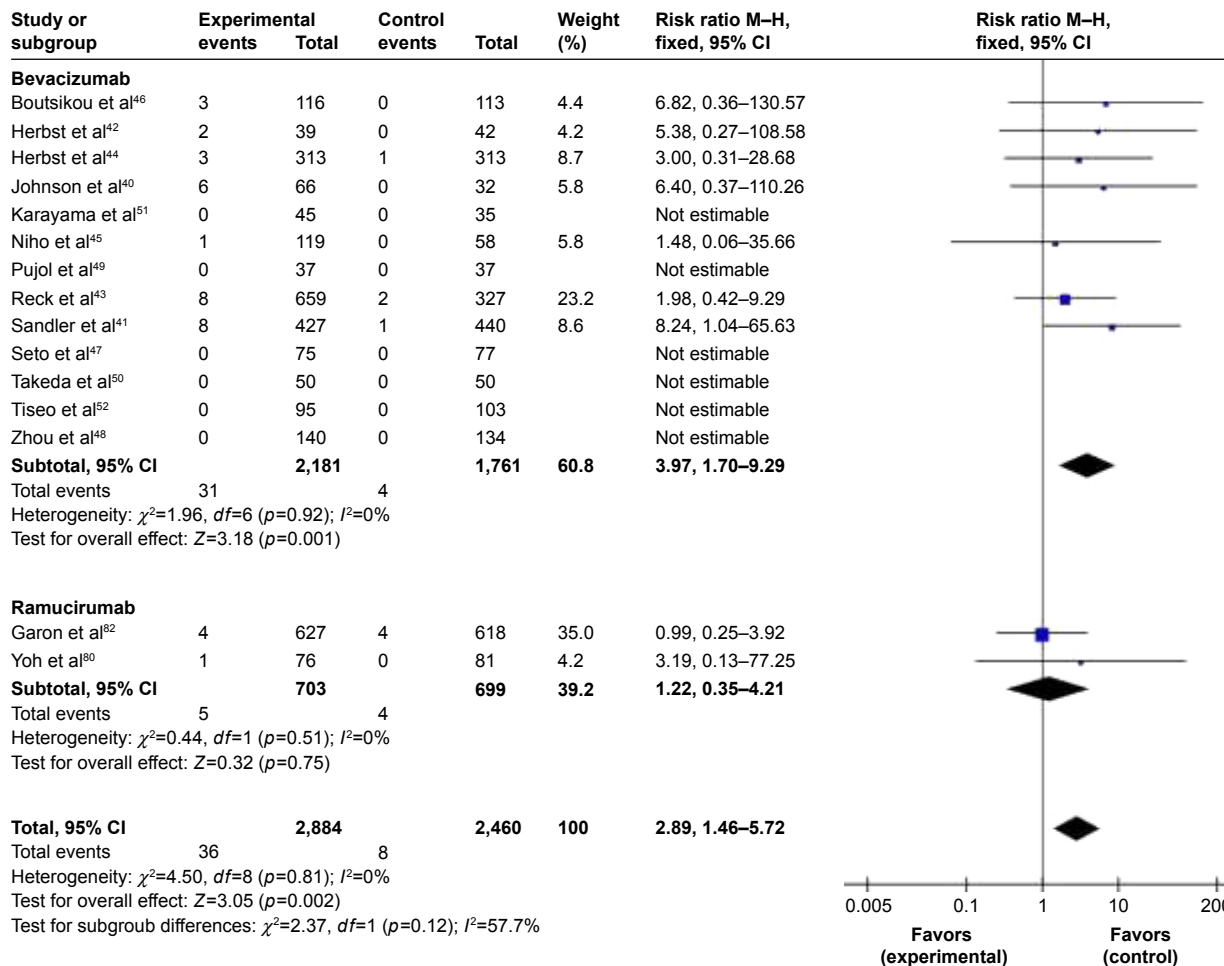


Figure 5 RR of high-grade pulmonary hemorrhage. Abbreviations: M-H, Mantel-Haenszel; RR, relative risk.

lung squamous cell carcinoma patients due to the small sample size or absence of original data. Finally, our literature search was limited to articles published in English leading to some selection bias.

Conclusion

Despite the limitations of our meta-analysis, we conclude that antiangiogenic monoclonal antibodies are associated with a significant increase in the risk of all-grade and high-grade bleeding. Ramucirumab may be different from bevacizumab in terms of the risk of high-grade bleeding and the risk of all-grade and high-grade pulmonary hemorrhage in lung cancer patients. Clinicians should be aware of this adverse effect and ensure close monitoring, especially in patients at high risk.

Acknowledgment

This study was supported by the Beijing Natural Science Foundation (7142125).

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3,4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	4,5
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7,8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7,8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	7,8

(Continued)



PRISMA 2009 Checklist (Continued)

Section/topic	#	Checklist item	Reported on page #
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see item 16]).	7,8
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	9,10
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10,11
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	11

Notes: Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097. For more information, visit: www.prisma-statement.org.

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