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Risk of Hypertension Associated with Antivascular Endothelial Growth Factor Monoclonal Antibodies: A Meta-Analysis From 51088 Patients with Cancer

Weilan Wang [#1], Le Cai [#1], Bingkun Xiao [2,*] and Rongqing Huang [2]

[1]Department of Pharmacy, Medical Supplies Center of Chinese PLA General Hospital, Beijing, China
[2]Department of Antiradiation Drug, Beijng Institute of Radiation Medicine, Beijing, China

[*]*Corresponding author*: Department of Antiradiation Drug, Beijng Institute of Radiation Medicine, Beijing, China. Tel/Fax: +86-1066930217, Email: 13161748010@163.com
# These authors are contributed equally as the first author.

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Abstract

Context: Hypertension events are the dominant adverse events observed in patients receiving the antivascular endothelial growth factor (anti-VEGF) monoclonal antibodies bevacizumab and ramucirumab treatment, which severe hypertension, particularly hypertensive emergencies, may cause acute target organ injury and major cardiovascular events, that has limited the administration of anti-VEGF monoclonal antibodies. The current meta-analysis aimed to examine the relative risk (RR) of hypertension associated with anti-VEGF monoclonal antibodies.
Evidence Acquisition: PubMed, EMBASE, ASCO Abstracts, ESMO Abstracts, Cochrane Library, and Clinical Trials.gov were searched until July 2019 for relevant phase II and III randomized controlled trials (RCTs). Statistical analyses were performed to examine the RR (with 95% confidence intervals (CIs)) of hypertension associated with the anti-VEGF monoclonal antibodies.
Results: Ninety four RCTs and 51088 patients were included in the current meta-analysis. According to the results, compared with the control arms, anti-VEGF monoclonal antibodies increased the risk of all-grade (RR: 3.45, 95% CI: 2.98 - 4.00) and high-grade (RR: 5.63, 95% CI: 5.05 - 6.26) hypertension. In the subgroup analyses, the risk of high-grade hypertension varied significantly with cancer type, so that the highest RR was for patients with ovarian cancer (17.27, 95% CI: 8.50 - 35.08), whereas the risk of all-grade hypertension did not vary significantly. When stratified based on drug types and drug dose, no significant difference was discovered.
Conclusions: Anti-VEGF monoclonal antibodies significantly increased the risk of hypertension. The risk may vary with tumor type. Clinicians should be aware of the adverse reaction and clinical monitoring as well as effective management of such situations, particularly for high-risk patients.

Keywords: Anti-VEGF Monoclonal Antibodies, Bevacizumab, Ramucirumab, Hypertension, Meta-Analysis

1. Context

Angiogenesis has an important role in promoting tumor growth, invasion, and metastasis. VEGF-A, one of the members of the vascular endothelial growth factor family, plays a vital role in angiogenesis and tissue neovascularization. Among all receptors, VEGFR-2 is widely considered as the most critical driver of tumor angiogenesis. Therefore, inhibition of angiogenesis via blocking VEGF-A or VEGFR-2 receptor signaling pathway is the key approach in current tumor therapeutics (1).

As a VEGF-A-targeted monoclonal antibody, bevacizumab widely administers in the treatment of various cancers. Ramucirumab is a VEGFR2- targeted monoclonal antibody and inhibits the signaling pathways in endothelial cells that mediate angiogenesis. Ramucirumab is approved for the treatment of advanced gastric, lung, and colorectal cancers.

Hypertension events are the most common adverse events of patients who receive the antivascular endothelial growth factor (anti-VEGF) monoclonal antibodies bevacizumab and ramucirumab treatment, which severe hypertension, particularly hypertensive emergencies may cause acute target organ injury and major cardiovascular events, that has limited the administration of anti-VEGF monoclonal antibodies (2). Previously conducted meta-analyses have investigated the risk of hypertension for bevacizumab or ramucirumab. However, the risk of hypertension caused by the anti-VEGF monoclonal antibodies is not yet evaluated systematically. Therefore, we performed the first meta-analysis to examine the risk of hypertension

associated with anti-VEGF monoclonal antibodies.

The current meta-analysis aimed to examine the risk of hypertension associated with anti-VEGF monoclonal antibodies.

2. Evidence Acquisition

2.1. Search Strategy

To conduct the current meta-analysis, using the "bevacizumab", "Avastin", "ramucirumab", "IMC1121B", "LY3009806", and "cancer" keywords, the following databases were searched: PubMed, ASCO abstracts, ESMO abstracts, and the clinical trial registration website (https://www.ClinicalTrials.gov) for relevant trials till July 2019. To ensure that all relevant clinical trials are incorporated into the meta-analysis, an independent search was conducted using the Web of Science databases.

2.2. Selection of Trials

The publications and data were reviewed and extracted by two independent investigators. Discrepancies were resolved by consensus with a third researcher. The randomized controlled trials that met the following criteria were included (1) phase II and III randomized controlled trials on cancer patients; (2) having a case group with anti-VEGF monoclonal antibodies treatment alone/concurrent chemotherapy or a control group with placebo/chemotherapy alone; and (3) Events or incidence and sample size available for hypertension.

2.3. Data Extraction

Data on study characteristics, therapeutic strategy, and results and reports of hypertension of all eligible studies were collected. The primary endpoint was the relative risk of hypertension with anti-VEGF monoclonal antibodies. Grading of hypertension events was based on versions 3.0 or 4.0 of Common Terminology Criteria.

2.4. Statistical Analysis

Analyses were performed using the RevMan 5.2. The heterogeneity of eligible studies was assessed by the I2 statistic. If $P \geq 0.1$ and $I2 \leq 50\%$, data were analyzed by the fixed-effects model, the analysis was conducted using the random-effects model. Subgroup analyses were performed separated by the drug type, dosage, and cancer type to explore possible reasons for heterogeneity. We performed a meta-regression analysis to investigate various variables on hypertension events by Stata version 12.0.

3. Results

3.1. Search Results

The initial literature review resulted in 2723 potentially relevant studies, of which 2491 were excluded because of the following reasons: reviews, commentaries, letters, basic studies, case reports, non-randomized controlled trials, irrelevant topics, and duplications. The 232 remaining studies were carefully screened and 138 studies were removed because both control and treatment groups were receiving anti-VEGF monoclonal antibodies or data required for assessment of hypertension were not available. The remaining 94 randomized controlled trials were judged as eligible for the purpose of the analysis (Figure 1).

3.2. Characteristics of Studies

94 RCTs and 51088 patients were selected for this meta-analysis, which were as follows 80 trials of bevacizumab (3 - 82) and 14 trials of ramucirumab (83 - 96) were investigated (3 - 82). All malignancies, including lung cancer (19 trials), colorectal cancer (22 trials), breast cancer (19 trials), ovarian cancer (4 trials), pancreatic cancer (2 trials), renal cell cancer (4 trials), gastric or gastro-oesophageal junction adenocarcinoma (7 trials), glioblastoma (3 trials), lymphoma (2 trials), melanoma (2 trials), lymphocytic leukemia (one trial), prostate cancer (one trial), two malignant mesothelioma (one trial), leiomyosarcoma (one trial), urothelial carcinoma (2 trials), hepatocellular carcinoma (one trial), multiple myeloma (one trial), and soft tissue sarcoma (one trial). The quality of all the trials included in the meta-analysis was acceptable. The characteristics of 94 trials are listed in Table 1.

3.3. RR of All-Grade Hypertension Events

To assess the relative risk of all-grade hypertension 58 RCTs were reviewed. The random-effects model ($I^2 = 72\%$) revealed that anti-VEGF monoclonal antibodies significantly increased the relative risk of all-grade (3.45, 95% CI: 2.98 - 4.00, $P < 0.00001$) hypertension compared to control arms (Figure 2).

3.4. RR of High-Grade Hypertension Events

The relative risk of high-grade hypertension was assessed by 91 RCTs. Using a fixed-effects model ($I^2 = 46\%$), anti-VEGF monoclonal antibodies significantly increased the relative risk of high-grade hypertension (5.63, 95% CI: 5.05 - 6.26, $P < 0.00001$) ($I^2 = 46\%$). (Figure 3).

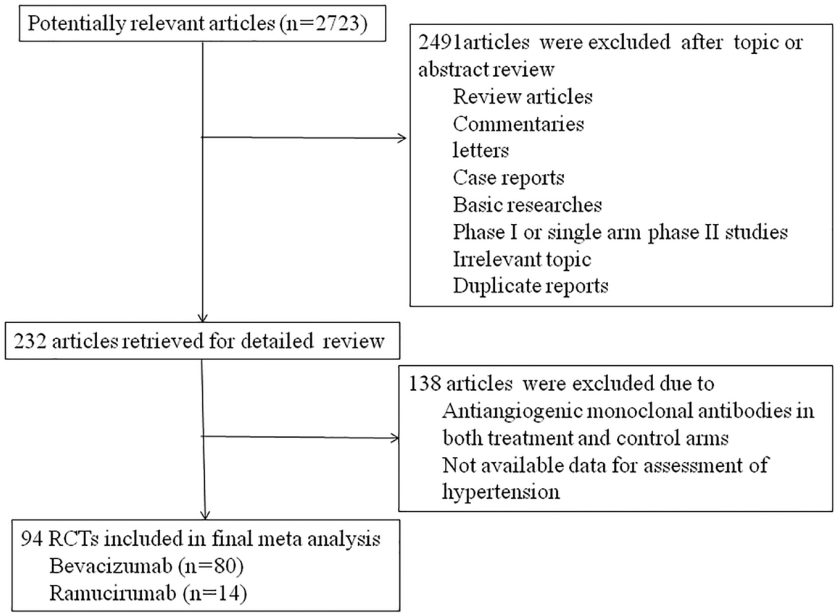

Figure 1. Outline of the search-flow diagram

3.5. Subgroup Analysis According to Drug Type

To explore the association between risk of hypertension events and drug type, a subgroup analysis was performed according to the type of the administered drug, which indicated the relative risk of all-grade hypertension events for bevacizumab (3.57: 95% CI: 2.98 - 4.28, P < 0.00001) and for ramucirumab (2.92: 95% CI: 2.42 - 3.52, P < 0.00001). No significant difference was observed between the subgroups (P = 0.571, Table 2).

For high-grade hypertension events, the relative risk (RR) was 6.04 (95% CI: 5.37 - 6.80, P < 0.00001) for bevacizumab and 3.83 (95% CI: 2.96 - 4.96, P < 0.00001) for ramucirumab. There was no significant difference (P = 0.224) between bevacizumab and ramucirumab (Table 3).

3.6. Subgroup Analysis According to Drug Dose

In the stratified analysis, which was performed according to the dose of anti-VEGF monoclonal antibodies, RR of all-grade hypertension for bevacizumab at 2.5 mg/kg/week was 3.13 (95% CI: 2.51 - 3.91), for bevacizumab at 5 mg/kg/week was 4.06 (95% CI: 3.09 - 5.34), for ramucirumab at 3.3 mg/kg/week was 2.53 (95% CI: 2.02 - 3.17), and for ramucirumab at 4 mg/kg/week was 3.21 (95% CI: 2.46 - 4.18). No significant difference was found by various drug doses (P = 0.408, Table 2).

For high-grade hypertension events, RR for bevacizumab at 2.5 mg/kg/week was 5.70 (95% CI: 4.66 - 6.97), for bevacizumab at 5mg/kg/week was 6.16 (95% CI: 5.34 - 7.11), for ramucirumab at 3.3mg/kg/week was 3.39 (95% CI: 2.26 - 5.08), and for ramucirumab at 4 mg/kg/week was 4.17 (95% CI: 2.98 - 5.83). No significant difference was observed by various drug dose (P = 0.369, Table 3).

3.7. Subgroup Analysis According to Cancer Type

In the subgroup analysis, which was performed according to the cancer type (i.e., ovarian cancer, renal cell carcinoma, and other cancer types), the risk of all-grade hypertension events was higher for these cancers. RR for ovarian cancer patients was 6.15 (95% CI: 3.34 - 11.35), for renal cell carcinoma patients was 4.02 (95% CI: 2.35 - 6.87), and for other tumor patients was 3.23 (95% CI: 2.76 - 3.76). However, RR of all-grade hypertension events did not vary significantly according to the cancer type (P = 0.074, Table 2).

For high-grade hypertension events, RR varied significantly (P = 0.003), the highest and lowest RR was for ovarian cancer patients (17.27, 95% CI: 8.50 - 35.08) and for other cancer patients (5.27, 95% CI: 4.72 - 5.88, Table 3), respectively.

3.8. Publication Bias

Funnel plots were performed to assess publication bias. No apparent publication bias was detected for all-grade and high-grade hypertension by the funnel plots.

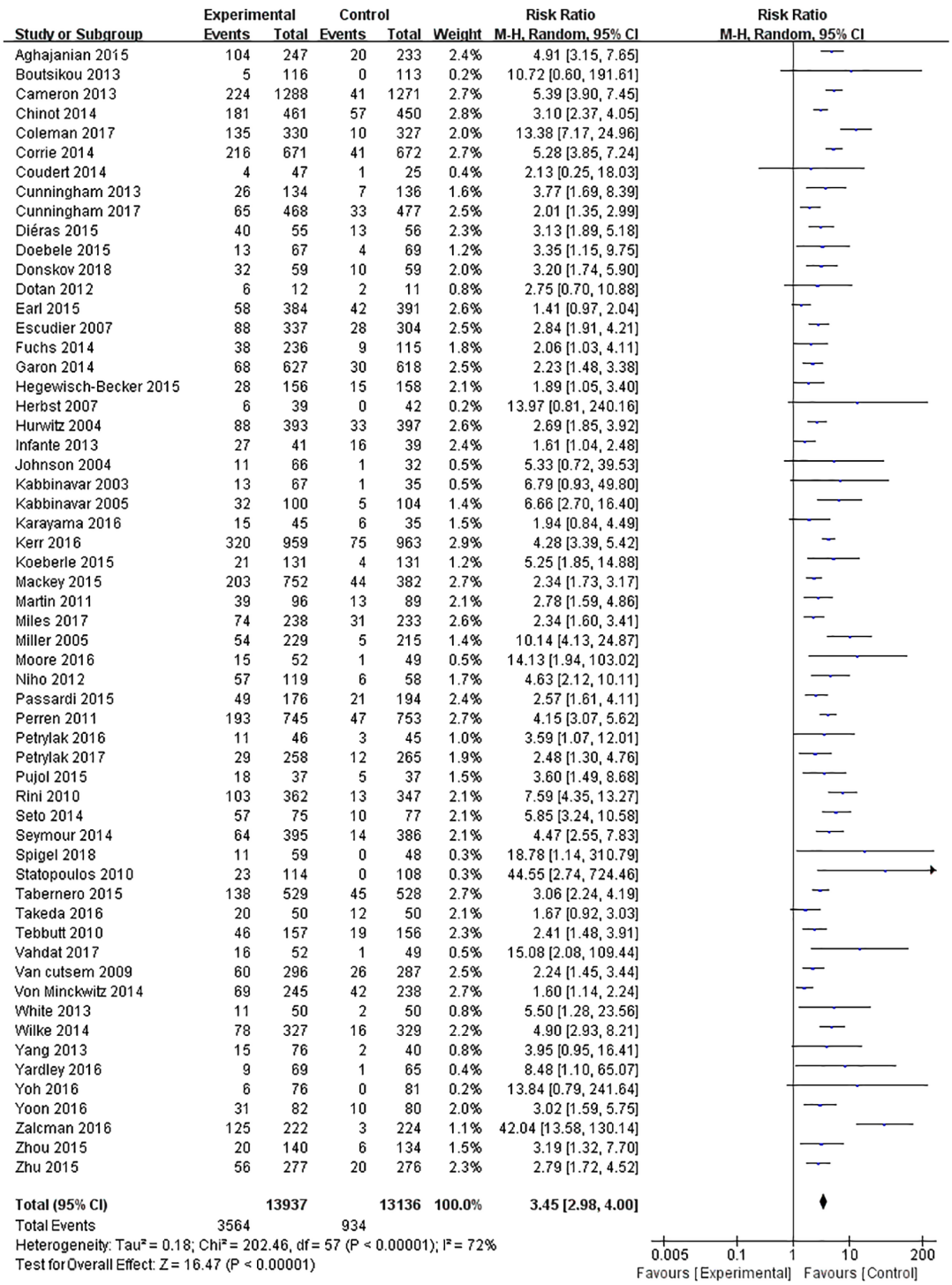

Figure 2. Forest plot of the relative risk of all-grade hypertension

4. Discussion

To the best of our knowledge, this is the first meta-analysis that examined the risk of hypertension events associated with anti-VEGF monoclonal antibodies.

Analysis of the data from RCTs demonstrated that anti-

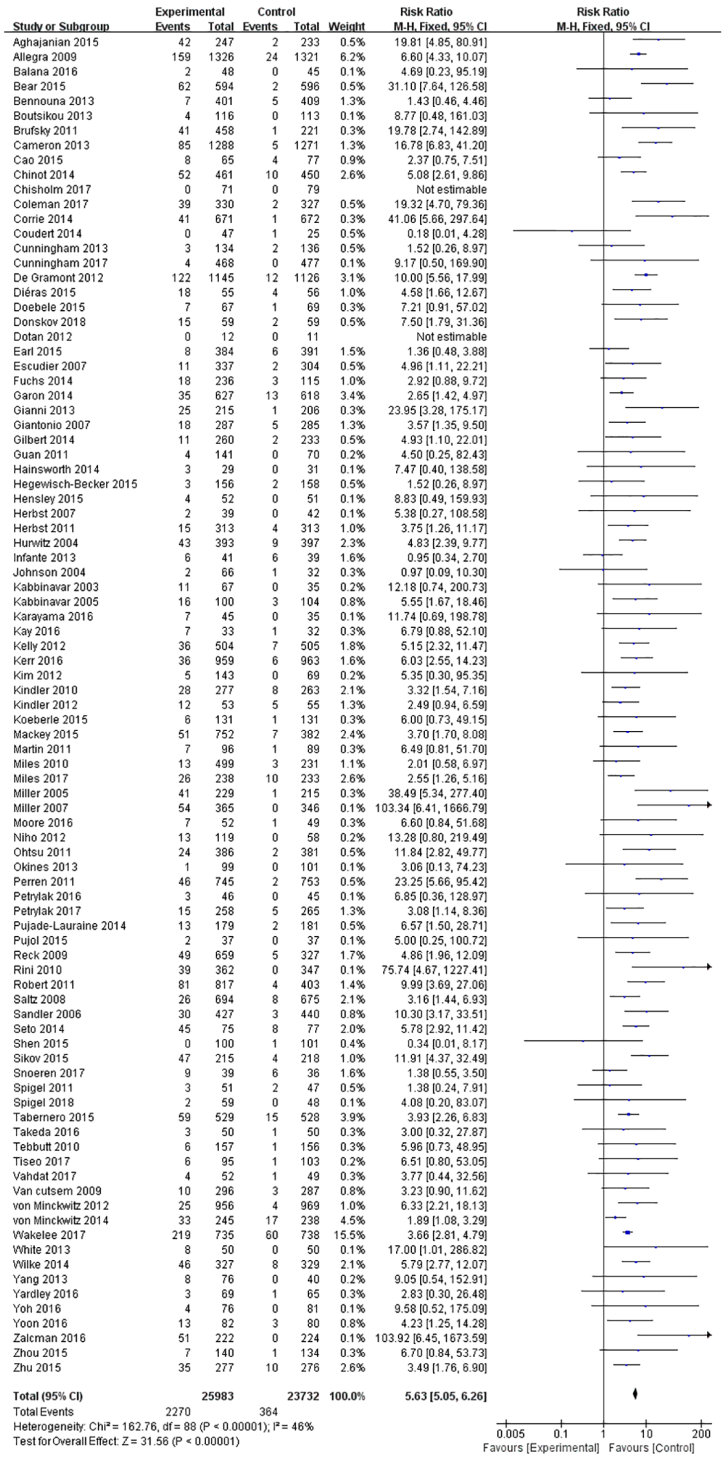

Figure 3. Forest plot of the relative risk of high-grade hypertension

VEGF monoclonal antibodies increase the risk of all-grade (RR: 3.45, 95% CI: 2.98 - 4.00) and high-grade (RR: 5.63, 95% CI: 5.05 - 6.26) hypertension compared to control arms. The mechanisms of hypertension induced by angiogenesis in-

Table 2. Relative Risk of All-Grade Hypertension Associated with Angiogenesis Inhibitors in the Subgroup Analysis

Hypertension	Number of Trials	Number of Events/Total		RR, 95% CI	P	P Value for Group Difference
		Treatment	Control			
Type of drug						0.571
Bev	44	2853/10487	738/10185	3.57 [2.98, 4.28]	< 0.00001	
Ram	14	711/3450	196/2951	2.92 [2.42, 3.52]	< 0.00001	
Drug dosage, mg/kg/week						0.408
Bev 2.5	19	1232/4773	351/4803	3.13 [2.51, 3.91]	< 0.00001	
Bev 5	27	1620/5677	389/5449	4.06 [3.09, 5.34]	< 0.00001	
Ram 3.3	8	355/1947	95/1574	2.53 [2.02, 3.17]	< 0.00001	
Ram 4	6	356/1503	101/1377	3.21 [2.46, 4.18]	< 0.00001	
Tumor types						0.074
OC	3	432/1322	77/1313	6.15 [3.34, 11.35]	< 0.00001	
RCC	4	238/834	53/750	4.02 [2.35, 6.87]	< 0.00001	
Other tumor	51	2894/11781	804/11073	3.23 [2.76, 3.76]	< 0.00001	

Abbreviations: Bev, bevacizumab; OC, ovarian cancer; Ram, ramucirumab; RCC, renal cell carcinoma.

Table 3. Relative Risk of High-Grade Hypertension Associated with Angiogenesis Inhibitors in the Subgroup Analysis

Hypertension	Number of Trials	Number of Events/Total		RR, 95% CI	P	P Value for Group Difference
		Treatment	Control			
Type of drug						0.224
Bev	77	1970/22533	296/20781	6.04 [5.37, 6.80]	< 0.00001	
Ram	14	300/3450	68/2951	3.83 [2.96, 4.96]	< 0.00001	
Drug dosage, mg/kg/week						0.369
Bev 2.5	30	619/9562	104/9461	5.70 [4.66, 6.97]	< 0.00001	
Bev 5	51	1351/12934	201/11945	6.16 [5.34, 7.11]	< 0.00001	
Ram 3.3	8	122/1947	28/1574	3.39 [2.26, 5.08]	< 0.00001	
Ram 4	6	178/1503	40/1377	4.17 [2.98, 5.83]	< 0.00001	
Tumor types						0.003
OC	4	140/1501	8/1494	17.27 [8.50, 35.08]	< 0.00001	
RCC	4	73/834	4/750	13.29 [5.44, 32.50]	< 0.00001	
Other tumors	83	2057/23648	352/21488	5.27 [4.72, 5.88]	< 0.00001	

Abbreviations: Bev, bevacizumab; OC, ovarian cancer; Ram, ramucirumab; RCC, renal cell carcinoma.

hibitor included increasing cell apoptosis, decreasing endothelial renewal capacity, suppressing the production of nitric oxide in vessels, and decreasing the number of capillaries and arterioles (2).

Because severe hypertension, particularly hypertensive emergencies, may cause acute target organ injury and major cardiovascular events, which in turn leads to limited administration of the anti-VEGF monoclonal antibodies. So, clinical monitoring and effective management might be important ways for the safe application of these agents.

To explore possible risk factors, subgroup analysis was performed according to the types of administered drugs. In the current meta-analysis, there was a higher risk of high-grade hypertension in patients using bevacizumab compared with ramucirumab (RR: 6.04 VS 3.83). However, no significant difference (P = 0.224) was discovered between bevacizumab and ramucirumab.

As a VEGF-A-targeted monoclonal antibody, beva-

cizumab prevents the activation of VEGFR-1 and VEGFR-2, whereas ramucirumab only inhibits the VEGFR-2 receptor. VEGFR-2 is a critical receptor for angiogenesis, and blockade of the VEGF-A/VEGFR-2 signaling may result in endothelial dysfunction and hypertension (2). The precise mechanism of VEGFR-1 is not entirely understood, and the study showed that VEGFR-1 tyrosine kinase signaling also had an effect on angiogenesis (97). Blockade of the VEGF-A/VEGFR-1 signaling resulted in the endothelial dysfunction and hypertension, but simultaneously played only a minor role compared with VEGF-A/VEGFR-2 signaling (98). This may be the reason for the higher risk of high-grade hypertension in patients who were receiving bevacizumab compared to those who were receiving ramucirumab; however, the difference was not statistically significant. The difference between bevacizumab and ramucirumab was more obvious for the risk of ATE, VTE, and high-grade bleeding (99).

Based on the results, all doses of angiogenesis inhibitors increase the risk of all-grade and high-grade hypertension events, but no significant difference was found between various doses of antiangiogenic monoclonal antibodies bevacizumab (2.5 mg/kg/week and 5 mg/kg/week) and ramucirumab (3.3 mg/kg/week and 4 mg/kg/week), no matter for the risk of all-grade hypertension (P = 0.408) or the risk of high-grade hypertension (P = 0.369), suggesting that the risk of hypertension events may not be dose-dependent.

In a meta-analysis on angiogenesis inhibitors, patients with renal cell carcinoma or ovarian cancer had a high risk of hypertension. Therefore, we performed subgroup analysis according to renal cell carcinoma, ovarian cancer, and other cancer types to identify potential risk factors. The risk of high-grade hypertension varied significantly according to the cancer type, with the highest and lowest RR was for ovarian cancer and other types of cancer. The underlying mechanisms of these differences are still unclear. A possible explanation is that patients with hypertension were not excluded from ovarian trials, despite antihypertensive treatment. Also, hypertension events are relatively common in women with ovarian cancer. The high incidence rate of hypertension may be related to cancer or its ovariectomy treatment. The depletion of endogenous estrogen by ovariectomy, at least in part, induces hypertension. For example, at least 40% of the participants of the OCEANS trial had baseline hypertension, and according to the literature, pre-existing hypertension predicts the increased risk for anti-VEGF therapy-induced hypertension (63). Besides, the RR of patients with renal cell carcinoma was times higher than those with other cancers. Although nephrectomy performed among renal cell carcinoma patients can decrease glomerular filtration, the concentration of antiangiogenic monoclonal antibodies is not be influenced by a decreased GFR likely, because the metabolism and elimination of these agents primarily rely on proteolytic catabolism throughout the body, and does not depend primarily on elimination through the kidneys and livers (2, 100). Thus, the possible explanation for this phenomenon is that post nephrectomy glomerular hypertrophy may be more dependent on VEGF to keep structural completeness than a normal kidney, leading to increased sensitiveness to angiogenesis inhibitors (101). So, patients with ovarian cancer or renal cell carcinoma should pay more attention to hypertension when receiving antiangiogenic monoclonal antibodies.

4.1. Limitations

One limitation of this meta-analysis is that we conducted subgroup analysis only for ovarian cancer, renal cell carcinoma, and other cancer types, mainly because it was difficult to assess so many cancer types included in the current meta-analysis. Besides, except for drug type, drug dose, and cancer type, other potential risk factors, such as age, race, sex, and treatment duration, could increase clinical heterogeneity and, therefore, were not evaluated in the study. Finally, the literature search was limited to articles published in English, which may have led to selection bias.

5. Conclusions

In conclusion, the results showed that anti-VEGF monoclonal antibodies significantly increased the risk of hypertension. The risk may vary with cancer type, in which the highest RR was for patients with ovarian cancer (17.27, 95% CI: 8.50 - 35.08). When patients were stratified based on the type of administered drugs and dosage, no significant difference was observed. Clinicians should be aware of the adverse reaction and clinical monitoring as well as effective management of such situations, particularly for high-risk patients.

Footnotes

Authors' Contribution: Bingkun Xiao was responsible for the idea and design for the meta-analysis. Weilan Wang and Le Cai contributed to data search and selection. Rongqing Huang carried out the statistical analyses.

Conflict of Interests: The authors declare no conflicts of interest.

Ethical Approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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Table 1. Characteristics of Studies Included in the Meta-Analysis

Author	Year	Malignancy	Phase	No in Intervention/Control	Concurrent Treatment	Dosemg/kg Per wk	No. Hypertension Events Intervention/Control	
							All Grade	Grade ≥ 3
					Bevacizumab			
Kabbinavar et al. (3)	2003	CRC	II	67/35	Fluorouracil + leucovorin	2.5 or 5	13/1	11/0
Hurwitz et al. (4)	2004	CRC	III	393/397	Irinotecan + fluorouracil + leucovorin	2.5	88/33	43/9
Kabbinavar et al. (5)	2005	CRC	II	100/104	Fluorouracil + leucovorin	2.5	32/5	16/3
Giantonio et al. (6)	2007	CRC	III	287/285	Oxaliplatin + fluorouracil + leucovorin	5	NR	18/5
Saltz et al. (7)	2008	CRC	III	694/675	Capecitabine + oxaliplatin/Fluorouracil + folinic acid + oxaliplatin	2.5	NR	26/8
Allegra et al. (8)	2009	CRC	III	1326/1321	Oxaliplatin + fluorouracil + leucovorin	2.5	NR	159/24
Tebbutt et al. (9)	2010	CRC	III	157/156	Capecitabine	2.5	46/19	6/1
Statopoulos et al. (10)	2010	CRC	III	114/108	Irinotecan + fluorouracil + leucovorin	2.5	23/0	NR
Guan et al. (11)	2011	CRC	III	141/70	Irinotecan + fluorouracil + leucovorin	2.5	NR	4/0
Dotan et al. (12)	2012	CRC	II	12/11	Capecitabine + oxaliplatin + cetuximab	2.5	6/2	0/0
de Gramont et al. (13)	2012	CRC	III	1145/1126	Oxaliplatin + fluorouracil + leucovorin	2.5	NR	122/12
Bennouna et al. (14)	2013	CRC	III	401/409	Fluorouracil/Capecitabine + Oxaliplatin/Irinotecan	2.5	NR	7/5
Cunningham et al. (15)	2013	CRC	III	134/136	Capecitabine	2.5	26/7	3/2
Infante et al. (16)	2013	CRC	II	41/39	Axitinib + oxaliplatin + fluorouracil + leucovorin	2.5	27/16	6/6
Cao et al. (17)	2015	CRC	II	65/77	Irinotecan + fluorouracil + leucovorin	5	NR	8/4
Hegewisch-Becker et al. (18)	2015	CRC	III	156/158	None	2.5	28/15	3/2
Passardi et al. (19)	2015	CRC	III	176/194	Irinotecan + fluorouracil + leucovorin/oxaliplatin + fluorouracil + leucovorin	2.5	49/21	NR
Koeberle et al. (20)	2015	CRC	III	131/131	None	2.5	21/4	6/1
Kerr et al. (21)	2016	CRC	III	959/963	Capecitabine	2.5	320/75	36/6
Snoeren et al. (22)	2017	CRC	III	39/36	Capecitabine + oxaliplatin	2.5	NR	9/6
Miller et al. (23)	2005	BC	III	229/215	Capecitabine	5	54/5	41/1
Miller et al. (24)	2007	BC	III	365/346	Paclitaxel	5	NR	54/0
Miles et al. (25)	2010	BC	III	499/231	Docetaxel	2.5 or 5	NR	13/3

Brufsky et al. (26)	2011	BC	III	458/221	Capecitabine/Taxane/Gemcitabine/Vinorelbine	5	NR	41/1
Robert et al. (27)	2011	BC	III	817/403	Capecitabine/Taxane/Anthracycline	5	NR	81/4
Martin et al. (28)	2011	BC	II	96/89	None	5	39/13	7/1
von Minckwitz et al. (29)	2012	BC	III	956/969	Docetaxel	5	NR	25/4
Gianni et al. (30)	2013	BC	III	215/206	Docetaxel + trastuzumab	5	NR	25/1
Cameron et al. (31)	2013	BC	III	1288/1271	Anthracycline/Taxane	5	224/41	85/5
Coudert et al. (32)	2014	BC	II	47/25	Trastuzumab + docetaxel	5	4/1	0/1
von Minckwitz et al. (33)	2014	BC	III	245/238	Taxane/Anthracycline/Capecitabine/Vinorelbine/(	5	69/42	33/17
Bear et al. (34)	2015	BC	III	594/596	Docetaxel-based chemotherapy	5	NR	62/2
Sikov et al. (35)	2015	BC	II	215/218	Doxorubicin + cyclophlsphamide ± carboplatin	5	NR	47/4
Earl et al. (36)	2015	BC	III	384/391	Docetaxel-Fluorouracil + epirubicin + cyclophosphamide	5	58/42	8/6
Dieras et al. (37)	2015	BC	II	55/56	Trebananib + Paclitaxel	5	40/13	18/4
Miles et al. (38)	2017	BC	III	238/233	paclitaxel	5	74/31	26/10
Johnson et al. (39)	2004	LC	II	66/32	Carboplatin + paclitaxel	2.5 or 5	11/1	2/1
Sandler et al. (40)	2006	LC	III	427/440	Paclitaxel + carboplatin	5	NR	30/3
Herbst et al. (41)	2007	LC	II	39/42	Docetaxel/pemetrexed	5	6/0	2/0
Reck et al. (42)	2009	LC	III	659/327	Cisplatin + gemcitabine	2.5 or 5	NR	49/5
Herbst et al. (43)	2011	LC	III	313/313	Erlotinib	5	NR	15/4
Spigel et al. (44)	2011	LC	II	51/47	cisplatin/carboplatin + etoposide	5	NR	3/2
Niho et al. (45)	2012	LC	II	119/58	Carboplatin + paclitaxel	5	57/6	13/0
Boutsikou et al. (46)	2013	LC	III	116/113	Docetaxel + carboplatin ± erlotinib	2.5	5/0	4/0
Seto et al. (47)	2014	LC	II	75/77	Erlotinib	5	57/10	45/8
Zhou et al. (48)	2015	LC	III	140/134	Carboplatin, paclitaxel	5	20/6	7/1
Pujol et al. (49)	2015	LC	II-III	37/37	Cisplatin + etoposide ± epidoxorubicin + cyclophosphamide	2.5	18/5	2/0
Takeda et al. (50)	2016	LC	II	50/50	Docetaxel	5	20/12	3/1
Karayama et al. (51)	2016	LC	II	45/35	Pemetrexed	5	15/6	7/0
Tiseo et al. (52)	2017	LC	III	95/103	Cisplatin + etoposide	2.5	NR	6/1
Wakelee et al. (53)	2017	LC	III	735/738	Cisplatin + vinorel-bine/docetaxel/gemcitabine/pemetrexed	5	NR	219/60
Spigel et al. (54)	2018	LC	II	59/48	pemetrexed	5	11/0	2/0
Yang et al. (55)	2003	RCC	II	76/40	None	1.5 or 5	15/2	8/0

Escudier et al. (56)	2007	RCC	III	337/304	Interferon alfa	5	88/28	11/2
Rini et al. (57)	2010	RCC	III	362/347	Interferon alfa	5	103/13	39/0
Donskov et al. (58)	2018	RCC	II	59/59	Interleukin-2 + interferon-a	5	32/10	15/2
Van cutsem et al. (59)	2009	PC	III	296/287	Gemcitabine + erlotinib	2.5	60/26	10/3
Kindler et al. (60)	2010	PC	III	277/263	Gemcitabine	5	NR	28/8
Perren et al. (61)	2011	OC	III	745/753	Paclitaxel + carboplatin	2.5	193/47	46/2
Pujade-Lauraine et al. (62)	2014	OC	III	179/181	PLD/paclitaxel/topoteca	5	NR	13/2
Aghajanian et al. (63)	2015	OC	III	247/233	Gemcitabine + carboplatin	5	104/20	42/2
Coleman et al. (64)	2017	OC	III	330/327	Paclitaxel + carboplatin	5	135/10	39/2
Ohtsu et al. (65)	2011	GC	III	386/381	Cisplatin + capecitabine	2.5	NR	24/2
Okines et al. (66)	2013	GC	II/III	99/101	Epirubicin + cisplatin + capecitabine	2.5	NR	1/0
Shen et al. (67)	2015	GC, GEJC	III	100/101	Capecitabine + cisplatin	2.5	NR	0/1
Cunningham et al. (68)	2017	GEJC	II/III	468/477	Epiribicin + cisplatin + capecitabine	2.5	65/33	4/0
Chinot et al. (69)	2014	Glioblaston	III	461/450	Radiotherapy + temozolomide	5	181/57	52/10
Gilbert et al. (70)	2014	Glioblastoma	III	260/233	None	5	NR	11/2
Balana et al. (71)	2016	Glioblaston	II	48/45	Temozolomide	5	NR	2/0
Hainsworth et al. (72)	2014	Lymphoma	II	29/31	Rituximab	5	NR	3/0
Seymour et al. (73)	2014	Lymphoma	III	395/386	Rituximab + doxorubicin + vincristine + cyclophosphamide + prednisone	5	64/14	NR
Kay et al. (74)	2016	lymphocytic leukemia	II	33/32	Pentostatin + cyclophosphamide + rituximab	5	NR	7/1
Kim et al. (75)	2012	Melanoma	II	143/69	Paclitaxel + carboplatin	5	NR	5/0
Corrie et al. (76)	2014	melanoma	III	671/672	None	2.5	216/41	41/1
Kindler et al. (77)	2012	MM	II	53/55	Gemcitabine + cisplatin	5	NR	12/5
Zalcman et al. (78)	2016	MM	III	222/224	Pemetrexed + cisplatin	5	125/3	51/0
Kelly et al. (79)	2012	Prostate cancer	III	504/505	Docetaxel + prednisone	5	NR	36/7
Hensley et al. (80)	2015	uLMS	III	52/51	Gemcitabine + docetaxel	5	NR	4/0
Chisholm et al. (81)	2017	STSs	II	71/79	Cyclophosphamide + Vinorelbine	2.5	NR	0/0
White et al. (82)	2013	multiple myeloma	II	50/50	Bortezomib	5	11/2	8/0
					Ramucirumab			
Garon et al. (83)	2014	LC	III	627/618	Docetaxel	3.3	68/30	35/13
Doebele et al. (84)	2015	LC	II	67/69	Pemetrexed + carboplatin/cisplatin	3.3	13/4	7/1

Yoh et al. (85)	2016	LC	II	76/81	Docetaxel	3.3	6/0	4/0
Petrylak et al. (86)	2016	UC	II	46/45	Docetaxel	3.3	11/3	3/0
Petrylak et al. (87)	2017	UC	III	258/265	Docetaxel	3.3	29/12	15/5
Tabernero et al. (88)	2015	CRC	III	529/528	Irinotecan + fluorouracil + leucovorin	4	138/45	59/15
Moore et al. (89)	2016	CRC	II	52/49	Oxaliplatin + fluorouracil + leucovorin	4	15/1	7/1
Mackey et al. (90)	2015	BC	III	752/382	Docetaxel	3.3	203/44	51/7
Yardley et al. (91)	2016	BC	II	69/65	Eribulin	3.3	9/1	3/1
Vahdat et al. (92)	2017	BC	II	52/49	Capecitabine	3.3	16/1	4/1
Fuchs et al. (93)	2014	GC or GEJC	III	236/115	None	4	38/9	18/3
Wilke et al. (94)	2014	GC or GEJC	III	327/329	Paclitaxel	4	78/16	46/8
Yoon et al. (95)	2016	GC, EC,or GEJC	II	82/80	Oxaliplatin + fluorouracil + leucovorin	4	31/10	13/3
Zhu et al. (96)	2015	HC	III	277/276	None	4	56/20	35/10

Abbreviations: BC, breast cancer; CRC, colorectal cancer; EC, esophagus cancer; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HC, hepatocellular carcinoma; LC, lung cancer; MM, malignant mesothelioma; NR, not reached; OC, ovarian cancer; PC, pancreatic cancer; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; STSs, soft tissue sarcomas; UC, urothelialcarcinoma; uLMS, uterine leiomyosarcoma.