

Clinical significance of hypertension in patients with different types of cancer treated with antiangiogenic drugs (Review)

MEI DONG^{1*}, RUJIAN WANG^{2*}, PING SUN², DONGXIA ZHANG¹,
ZHENZHEN ZHANG¹, JING ZHANG¹, GARY TSE³ and LIN ZHONG¹

Departments of ¹Cardiology and ²Oncology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, Shandong 264000; ³Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin 300211, P.R. China

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Abstract. Hypertension is a common comorbidity in patients receiving antiangiogenic therapy. Prior studies have reported worsening or new-onset hypertension as an adverse event of antiangiogenic therapy, which can be managed by dose reduction or discontinuation of the culprit medication. By contrast, other studies have found that the occurrence of hypertension is a potential biomarker associated with greater efficacy of antiangiogenic therapy and predicts improved survival. At present, there is no consensus on the effects of hypertension in patients treated with antiangiogenic drugs. The present study reviewed the relationship between antiangiogenic drugs and hypertension in different types of cancer. It was demonstrated that the use of antiangiogenic drugs was associated with an increased risk of hypertension in most types of solid cancers. There was no significant difference in the incidence of hypertension between monoclonal antibody and small-molecule tyrosine kinase inhibitor treatments. Hypertension was more likely to occur in patients younger than 75 years old, female, and those with no history of bevacizumab use. Discontinuation or death caused by hypertension was rare, although previous studies have reported that hypertension was a risk factor for acute and chronic cardiovascular diseases and ischemic stroke. Of note, the early development of hypertension may serve as a potential

biomarker associated with greater efficacy of antiangiogenic therapy.

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1. Introduction

Angiogenesis is a crucial enabling process for tumor growth and metastasis (1). The vascular endothelial growth factor (VEGF) signaling pathway serves a key role in the angiogenesis of solid tumors. The VEGF signaling system is complex and consists of five related ligands: VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor (PLGF). They bind with different specificities to three receptor tyrosine kinases: VEGFR1, VEGFR2 and VEGFR3 (2). VEGF pathway-targeting agents include monoclonal antibodies, such as bevacizumab and ramucirumab, and small-molecule tyrosine kinase inhibitors (TKIs), such as sunitinib, sorafenib, apatinib and regorafenib. Monoclonal antibodies block the binding of VEGF to VEGFR and prevent activation of intracellular signal transduction (3). Small-molecule TKIs act on the intracellular domain of the endothelial receptor, where they inhibit the initial phosphorylation step following the ligand-receptor interaction (4). These drugs can slow down the growth of tumors effectively

Correspondence to: Dr Lin Zhong, Department of Cardiology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, 20 Yuhuangding East Road, Yantai, Shandong 264000, P.R. China
E-mail: yizun1971@126.com

Dr Gary Tse, Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, 23 Pingjiang Road, Tianjin 300211, P.R. China
E-mail: gary.tse@doctors.org.uk

*Contributed equally

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and improve the progression-free survival (PFS) and overall survival (OS) of patients with cancer (2).

However, a previous study has reported that antiangiogenic therapy increased arterial blood pressure (BP), raised the risk of new-onset hypertension, or worsened existing hypertension (5). The mechanism underlying the antiangiogenic drug-induced hypertension remains controversial. The current hypotheses include decreased nitric oxide (NO) (6), increased endothelin-1 (7), capillary rarefaction (8) and activation of the renin-angiotensin-aldosterone system (RAAS) (9) (Fig. 1). According to the National Cancer Institute's common terminology criteria for adverse events (NCI CTCAE), version 5.0 (10), hypertension for adults can be classed into five categories depending on its severity (Table I). Subsequently, the presence of hypertension can lead to a reduction or interruption of antiangiogenic therapy (11).

Considering the complex relationship between antihypertensive drugs and cancer, the cancer type, the pre-existing comorbidities and the presence of contraindications should be considered when selecting antihypertensive drugs for patients with cancer (12). Currently, angiotensin-converting enzyme inhibitors (ACEIs) are the preferred first-line option in treatment of hypertension induced by anti-VEGF chemotherapy, given its improved outcome in several types of cancer (13). On the other hand, several retrospective studies (14,15) have found that the appearance of hypertension during antiangiogenic therapy might be associated with improved survival. Thus, it remains unclear whether hypertension should be considered as an adverse reaction or as a positive prognostic marker in patients with various types of cancer. The present review aimed to explore the relationship between hypertension and antiangiogenic therapy in different types of tumors.

2. Relationship between antiangiogenic therapy and hypertension in renal cell cancer

In total, nine studies have reported the association between hypertension and antiangiogenic drugs, including sunitinib, bevacizumab, sorafenib, axitinib and pazopanib, in renal cell carcinoma (RCC). Of these nine studies, seven were prospective studies (16-22) and two were retrospective studies (23,24), involving a total of 6,083 patients (Table II).

Hypertension as an adverse event of antiangiogenic therapy. Four phase III, randomized, double-blind, placebo-controlled trials (16-18,20) and a phase II, randomized, double-blind trial (19) demonstrated that antiangiogenic drugs increased the risk of hypertension in patients with RCC. Increased BP due to axitinib gradually dropped to baseline after the end of treatment (19). The incidence of hypertension in the TKI treatment group (33.2%) was higher compared with the group treated with monoclonal antibodies (27.4%). It is worth noting that the axitinib group had the highest incidence of severe hypertension [\geq grade (G) 3 hypertension]. Compared with the aforementioned studies, hypertension was more frequently observed in the Donskov *et al* study (24), which could be attributed to the different definition of hypertension used. Furthermore, the risk of hypertension may be dose-dependent (19), however, no association with nephrectomy was observed (16). Thus, further research is needed to provide more evidence for the association

between antiangiogenic treatment and the risk of hypertension in patients with RCC.

Hypertension as a biomarker of antiangiogenic therapy. Two studies (22,23) found that significant hypertension (\geq G2) may be a potential biomarker associated with greater efficacy. In addition, another study using real-world data from Japan demonstrated that patients with hypertension have a higher 24-week OS and PFS rate (21). Donskov *et al* (24) found that on-treatment hypertension is an independent biomarker of sunitinib efficacy. These studies did not report the median time of hypertension-onset. However, Goldstein *et al* (25) found that hypertension caused by pazopanib or sunitinib was not a biomarker in the treatment of metastatic RCC.

3. Relationship between antiangiogenic therapy and hypertension in gastric cancer and gastroesophageal junction cancers

As an adjuvant treatment of gastric cancer, antiangiogenic drugs significantly prolong the survival of patients with advanced or metastatic gastric cancer (GC) in addition to gastroesophageal junction carcinoma (GEJ), and hypertension is a common adverse reaction that cannot be ignored. Five studies have reported the association between hypertension and antiangiogenic drugs, including apatinib and ramucirumab, of which, four were prospective studies (26-29) and one was a retrospective study (15). In total, 1,700 patients were included (Table III).

Hypertension as an adverse event of antiangiogenic therapy. Two double-blind, randomized, placebo-controlled, phase III trials for ramucirumab (27,28) and the phase II and III studies for apatinib (26,29) showed that ramucirumab and apatinib increased the risk of \geq G3 hypertension in patients with GC or GEJ carcinoma. The incidence of hypertension in the TKI treatment group (36.80%) was higher compared with the group treated with monoclonal antibodies (22.78%). However, the incidence of severe hypertension in the monoclonal antibody treatment group (11.37%) was higher compared with the TKI-treated group (6.32%). Of note, the incidence of severe hypertension was higher in the dose of 425 mg twice daily compared with the dose of 850 mg once-daily regimen (26), but this comparison lacked statistical significance.

Hypertension as a biomarker of effective antiangiogenic therapy. A retrospective cohort study of 269 patients demonstrated that the presence of hypertension within the first four weeks of antiangiogenic therapy was associated with prolonged median overall survival (15), suggesting that hypertension is an early prognostic marker. However, further studies are required to support this conclusion.

4. Relationship between antiangiogenic therapy and hypertension in lung cancer

Bevacizumab is the most widely used antiangiogenic drug for lung cancer treatment. Twelve studies have reported the association between hypertension and approved antiangiogenic drugs, including fruquintinib, crediranib, anlotinib and bevacizumab.

Table I. Definitions of hypertension grades for adults according to the National Cancer Institute's common terminology criteria for adverse events version 5.0.

Grade	Definition	Treatment
1	Systolic BP 120-139 mm Hg or diastolic BP 80-89 mmHg	NR
2	Systolic BP 140-159 mm Hg or diastolic BP 90-99 mm Hg if previously within normal level; Recurrent or persistent (≥ 24 h); Symptomatic increase by >20 mm Hg (diastolic) or to $>140/90$ mm Hg	Monotherapy or change in baseline medical intervention
3	Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg	NR
4	Life-threatening consequences (for example, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Urgent intervention
5	Death	-

BP, blood pressure; NR, not reported.

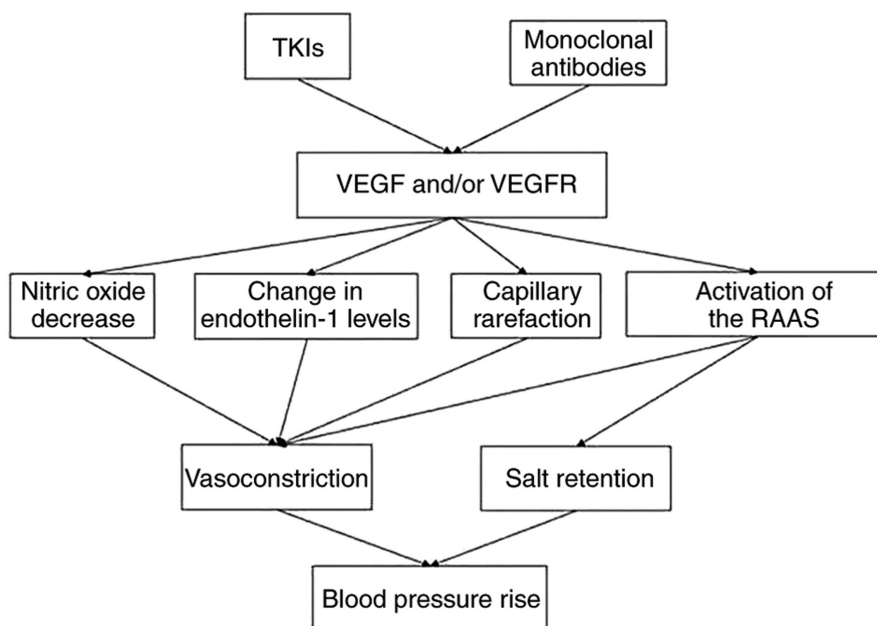


Figure 1. Possible mechanism of hypertension induced by antiangiogenic drugs. Monoclonal antibodies block the binding of VEGF to VEGFR, then prevent activation of intracellular signal transduction. Small-molecule TKIs act on the intracellular domain of the VEGFR, where they inhibit the initial phosphorylation step after the ligand-receptor interaction. Blocking the effect of VEGF/VEGFR can inhibit the production of nitric oxide, change the levels of endothelin-1 and reduce the production of capillaries. These effects induce vasoconstriction and inhibit tumor growth and metastasis, but at the same time, vasoconstriction also promotes the increase of blood pressure. In addition, several studies have shown that blocking the VEGF/VEGFR pathway can activate the RAAS, promote water and sodium retention, and raise blood pressure. VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; TKIs, tyrosine kinase inhibitors; RAAS, renin-angiotensin-aldosterone system.

There are seven prospective studies (30-36), two retrospective studies (14,37) and three meta-analyses (38-40). A total of 1,1291 patients were included (Table IV).

Hypertension as an adverse event of antiangiogenic therapy. Bevacizumab increased the risk of severe hypertension in the high-dose group (15 mg/kg) (32,39) and amongst female patients (41). There was no significant difference between different races (30), pathological types (38) and age (42). Discontinuation of medication due to hypertension was extremely rare (30,39). Based on these data, it was found in the present study that the incidence of hypertension in the

TKI treatment group (59.72%) was higher compared with the group treated with the monoclonal antibodies (28.61%). The incidence of hypertension was the highest in the anlotinib group (67.3%). A total of 13.6% patients developed severe hypertension during therapy. Notably, 23% of patients developed severe hypertension when receiving bevacizumab plus erlotinib (34).

Hypertension as a biomarker of antiangiogenic therapy. Two studies of bevacizumab (14,37) and one study of cediranib (36) suggested that the early development of hypertension was associated with clinical benefit.

Table II. Association between antiangiogenic drugs and hypertension in renal cell cancer.

Authors, year	Study type	Phase	Treatment lines	Sample size	Drug	Dose and frequency	Definition of HTN	Incidence of HTN and \geq G3 HTN	Main finding	Refs.
Ravaud <i>et al.</i> , 2016	Prospective study	III	First-line after nephrectomy	615	Sunitinib (309) vs. placebo (306)	50 mg, qd, 4 weeks on, 2 weeks off	CTCAE	36.9 and 7.8%	Sunitinib increased the risk of \geq G3 HTN	(16)
Escudier <i>et al.</i> , 2007	Prospective study	III	First-line	649	Bevacizumab + IFN- α -2a (327) vs. placebo + IFN- α -2a (322)	10 mg/kg, every two weeks	CTCAE	26 and 3%	Bevacizumab increased the risk of \geq G3 HTN	(17)
Escudier <i>et al.</i> , 2007	Prospective study	III	Second-line	903	Sorafenib (451) vs. placebo (452)	400 mg, bid	CTCAE	17 and 4%	Sorafenib increased the risk of \geq G3 HTN	(18)
Rini <i>et al.</i> , 2013	Prospective study	II	First-line	213	Axitinib (56) vs. placebo (56)	7 mg and then 10 mg, bid	CTCAE	61 and 18%	Axitinib increased the risk of \geq G3 HTN	(19)
Sternberg <i>et al.</i> , 2010	Prospective study	III	NR	435	Pazopanib (290) vs. placebo (145)	NR	CTCAE	40 and 4%	Pazopanib increased the risk of \geq G3 HTN	(20)
Akaza <i>et al.</i> , 2015	Prospective study	NR	NR	1'671	Sunitinib	50 mg, once daily	CTCAE	35 and 10%	HTN is potential biomarker for improved survival	(21)
Ravaud and Sire, 2009	Retrospective study	NR	NR	95	Sunitinib Sorafenib Bevacizumab	NR	CTCAE	NR	Significant hypertension predicted clinical benefit	(23)
Rini <i>et al.</i> , 2010	Prospective study	III	NR	732	Bevacizumab + IFN- α (369) vs. IFN- α (363)	10 mg/kg every 2 weeks	CTCAE	28 and 11%	Bevacizumab increased the risk of \geq G3 HTN and the development of HTN was an independent predictor of overall survival	(22)
Donskov <i>et al.</i> , 2015	Retrospective study	NR	NR	770	Sunitinib	NR	SBP \geq 140 mmHg	80%	Hypertension is independent biomarker of sunitinib efficacy	(24)

HTN, hypertension; G3, grade3; CTCAE, common terminology criteria for adverse events; NR, not reported; IFN- α , interferon- α ; SBP, systolic blood pressure. qd, once daily; bid, twice daily.

Table III. Association between anti-angiogenic drugs and hypertension in gastric and gastroesophageal junction cancer.

Authors, year	Study type	Phase	Treatment lines	Sample size	Drug	Dose and frequency	Definition of HTN	Incidence of HTN and \geq G3 HTN	Main finding	Refs.
Li <i>et al</i> , 2013	Prospective study	II	Third or greater the risk of \geq G3 HTN	144	Apatinib (96) vs. placebo (48)	425 mg bid or 850 mg qd	CTCAE	39.13% or 40.43% and 8.51% or 10.87%	Sunitinib increased	(26)
Fuchs <i>et al</i> , 2014	Prospective study	III	Second-line	355	Ramucirumab (238) vs. placebo (117)	8 mg/kg every 2 weeks	CTCAE	16 and 8%	Ramucirumab increased the risk of \geq G3 HTN	(27)
Wilke <i>et al</i> , 2014	Prospective study	III	Second-line	665	Ramucirumab + paclitaxel (330) vs. placebo + paclitaxel (335)	8 mg/kg, day 1,15	CTCAE	24 and 14%	Ramucirumab increased the risk of \geq G3 HTN	(28)
Li <i>et al</i> , 2016	Prospective study	III	Third or greater	267	Apatinib (176) vs. placebo (91)	850 mg qd	CTCAE	35.2 and 4.5%	Apatinib increased the risk of \geq G3 HTN	(29)
Liu <i>et al</i> , 2017	Retrospective cohort study	NR	NR	269	Apatinib	850 mg qd	CTCAE	NR	Presence of HTN was a biomarker of antitumor efficacy	(15)

HTN, hypertension; G3, grade 3; CTCAE, common terminology criteria for adverse events; NR, not reported. qd, once daily; bid, twice daily.

Table IV. Association between antiangiogenic drugs and hypertension in lung cancer.

Authors, year	Study type	Phase	Treatment lines	Patients	Drug	Dose and frequency	Definition of HTN	Incidence of HTN and \geq G3 HTN	Main finding	Refs.
Zhou <i>et al.</i> , 2015	Prospective study	III	First-line	276	Bevacizumab + PC (138) vs. placebo + PC (138)	15 mg/kg, every 21 days	CTCAE	14 and 5%	Bevacizumab increased the risk of HTN	(30)
Lin <i>et al.</i> , 2017	Meta-analysis	NR	NR	1,898	Bevacizumab, rh-Endostatin, Vandetanib, Thalidomide, Ziv-aflibercept	NR	CTCAE	NR	Anti-angiogenic drugs increased the risk of \geq G3 HTN	(38)
Sun <i>et al.</i> , 2015	Meta-analysis	First and second-line	First and second-line	3,284	Bevacizumab	NR	NR	NR	Bevacizumab increased the risk \geq G3 HTN	(39)
Sandler <i>et al.</i> , 2006	Prospective study	III	First-line	878	Bevacizumab + PC (440) vs. PC (427)	15 mg/kg, every 21 days	NR	NR and 7%	Bevacizumab increased the risk of \geq G3 HTN	(31)
Reck <i>et al.</i> , 2009	Prospective study	III	First-line	1,043	Bevacizumab + CG (696) vs. placebo+ CG (347)	7.5 or 15 mg/kg, every 21 days	CTCAE	6% or 9% ^a	Bevacizumab increased the risk of \geq G3 HTN	(32)
Lu <i>et al.</i> , 2018	Prospective study	II	Third-line	91	Fruquintinib (61) vs. placebo (30)	5 mg qd	CTCAE	23 and 8.2%	Fruquintinib increased the risk of \geq G3 HTN	(33)
Soria <i>et al.</i> , 2013	Meta-analysis	First-line	First-line	2,194	Bevacizumab	NR	NR	NR	Bevacizumab increased the risk of \geq G3 HTN	(40)
Saito <i>et al.</i> , 2019	Prospective study	III	NR	228	Bevacizumab + ertotinib (114) vs. ertotinib (114)	15 mg/kg, every 21 days	CTCAE	46 and 23%	Bevacizumab increased the risk of \geq G3 HTN	(34)
Zhou <i>et al.</i> , 2019	Prospective study	III	Third-line	437	Anlotinib (294) vs. placebo (143)	12 mg, qd, 2-week on and 1-week off	NR	67.3 and 13.6%	Anlotinib increased the risk of \geq G3 HTN	(35)
Koyama, 2014	Retrospective study	NR	NR	34	Bevacizumab	15 mg/kg, every 21 days	CTCAE	29 and 5.9%	Hypertension may be a prognostic factor for clinical outcome	(37)
Nakaya <i>et al.</i> , 2016	Retrospective study	NR	NR	632	Bevacizumab	15 mg/kg, every 21 days	CTCAE	NR	HTN may be a predictive marker for the efficacy	(14)
Goodwin <i>et al.</i> , 2010	Prospective study	II	NR	296	Crediranib	30 or 45 mg/day	CTCAE	NR	HTN was favorably prognostic factor for clinical outcome	(36)

^aIncidence of \geq G3 HTN in group of 7.5 mg/kg vs. group of 15 mg/kg. HTN, hypertension; G3, grade 3; PC, paclitaxel-carboplatin; CTCAE, common terminology criteria for adverse events; CG, cisplatin plus gemcitabine. rh-endostatin, recombinant human endostatin; qd, once daily; bid twice daily.

5. Relationship between antiangiogenic therapy and hypertension in colorectal cancer

Antiangiogenic therapy improved the overall survival of patients with colorectal cancer, but its benefit is offset partially by adverse events, such as hypertension. Thirteen studies have reported significant associations between hypertension and antiangiogenic drugs, including bevacizumab, ramucirumab and fruquintinib. There are six prospective studies (43-48), three retrospective studies (14,49,50), three meta-analyses (51-53) and one cohort study (54), including a total of 22,639 patients (Table V).

Hypertension as an adverse event of antiangiogenic therapy. A meta-analysis of 10,180 participants treated with bevacizumab (51), two randomized controlled studies for regorafenib (47) and a phase III controlled trial for ramucirumab (55) showed that these drugs increased the incidence of severe hypertension in patients with colorectal cancer. Hypertension caused by antiangiogenic drugs was associated with age (43,56,57) and regimen (58), but no association was observed with VEGF-D levels (55), race (59), cancer stage (45) or treatment line (47,48). Based on the aforementioned studies, the incidence of severe hypertension in the monoclonal antibodies group (13.11%) was higher than the TKI group (9.14%). Notably, bevacizumab was less likely to induce severe hypertension in elderly patients (age, ≥ 75 years) (43,56,57).

Hypertension as a biomarker of antiangiogenic therapy. Three retrospective studies (14,49,50) and a cohort study (54) of bevacizumab showed that early developing hypertension may be a predictive marker for the efficacy of bevacizumab.

Examples of trials that did not increase the risk of hypertension. Other studies have reported that bevacizumab did not significantly increase the risk of severe hypertension in patients receiving the drug (60,61) and patients who were aged ≥ 70 (57). However, the former conclusion may have selection bias, because amongst the patients who have previously received bevacizumab treatment, only patients who have not developed severe hypertension receive bevacizumab treatment again.

6. Relationship between antiangiogenic therapy and hypertension in hepatocellular carcinoma

Antiangiogenic drugs have an important role in the treatment of hepatocellular carcinoma (62). Five studies have reported the association between hypertension and antiangiogenic drugs, including cabozantinib, regorafenib, sorafenib and ramucirumab, in hepatocellular carcinoma. There are four prospective studies (63-66) and one retrospective study (67). A total of 2,272 patients were included (Table VI).

Hypertension as an adverse event of antiangiogenic therapy. Four phase III, randomized, double-blind, placebo-controlled trials of antiangiogenic drugs, including cabozantinib, regorafenib and ramucirumab, reported an increasing risk of severe hypertension in the drug-treated group, with an incidence of 13-16% (63-66). Based on the given data, it was found in the

present study that the incidence of severe hypertension in the TKI-treated group (14.51%) was moderately greater compared with the monoclonal antibodies-treated group (13.66%).

Hypertension as a biomarker of antiangiogenic therapy. One retrospective study of 38 patients suggested that hypertension within two weeks of therapy initiation may be a positive predictor of the anticancer efficacy of sorafenib in patients with hepatocellular carcinoma (67).

Examples of trials that did not increase the risk of hypertension. Three multicenter, phase III, double-blind, placebo-controlled trials showed that sorafenib did not significantly increase the risk of severe hypertension in patients with advanced hepatocellular carcinoma (68-70). This may be a unique manifestation of sorafenib in hepatocellular carcinoma.

7. Relationship between antiangiogenic therapy and hypertension in breast cancer

Antiangiogenic agents have been used extensively for the treatment of breast cancer, but high rates of treatment-induced hypertension have been reported (71). Six studies have reported the association between hypertension and antiangiogenic drugs including, bevacizumab and axitinib, in breast cancer. There are four prospective studies (72-75), one retrospective study (76) and one meta-analysis (77), with a total of 7,414 patients included (Table VII).

Hypertension as an adverse event of antiangiogenic therapy. A meta-analysis of five clinical trials reported that bevacizumab increased the risk of severe hypertension (77). Severe hypertension was more frequent in the high-dose group (73) and in some specific genotypes (76). In specific, Schneider *et al* (76) demonstrated that those with VEGF-1498TT and VEGF-634CC genotypes were largely protected from severe hypertension. There was no clear correlation between severe hypertension and baseline blood pressure (78). Based on the given data, it was found in the present study that the incidence of severe hypertension in the TKI-treated group (17.5%) was higher compared with the monoclonal antibodies-treated group (6.6%).

Hypertension as a biomarker of antiangiogenic therapy. Biomarker analysis of the Eastern Cooperative Oncology Group clinical trial E2100 demonstrated that patients with severe hypertension had a superior median overall survival, and that the VEGF-2578 AA genotype was associated with improved outcome (76). Another study of apatinib showed that the predictive effect of hypertension was not related to the grade of hypertension (75).

8. Discussion

The present brief review examined the association between hypertension and antiangiogenic therapy in different types of cancer. There are several key findings reported in the present review. First, the use of antiangiogenic drugs was associated with an increased risk of hypertension in most types of solid cancer. Based on the analyzed data, the incidence of hypertension (33.39%) was the highest in lung cancer. In addition, the

Table V. Association between antiangiogenic drugs and hypertension in colorectal cancer.

Authors, year	Study type	Phase	Treatment lines	Sample size	Drug	Dose and frequency	Definition of HTN	Incidence of HTN and \geq G3 HTN	Main finding	Refs.
Price <i>et al.</i> , 2012	Prospective study	NR	NR	471	Bevacizumab + CT (315) vs. CT (156)	NR	CTCAE	5.5% or 3.2% ^a	Bevacizumab didn't increase the risk of HTN in elderly patients (\geq 75 years), but increased the risk in young patients (<75 years)	(43)
Aparicio <i>et al.</i> , 2018	Prospective study	II	NR	102	Bevacizumab + CT (51) vs. CT (51)	NR	NR	NR and 13.7%	Bevacizumab increased the risk of \geq G3 HTN	(44)
Da Silva <i>et al.</i> , 2018	Meta-analysis	NR	NR	10,180	Bevacizumab Cetuximab	NR	CTCAE	NR	Anti-angiogenic drugs increased the risk of \geq G3 HTN	(51)
Hurwitz <i>et al.</i> , 2013	Meta-analysis	II-III	First and second line	3,763	Bevacizumab	5, 7.5 or 10 mg/kg	CTCAE	NR	Bevacizumab increased the risk of \geq G3 HTN	(52)
Allegra <i>et al.</i> , 2009	Prospective study	III	NR	2,710	Bevacizumab + CT (1354) vs. CT (1356)	5 mg/kg, every two weeks	CTCAE	NR and 12%	Bevacizumab increased the risk of \geq G3 HTN	(45)
Tabernero <i>et al.</i> , 2015	Prospective study	III	Second-line	1,072	Ramucirumab + CT (536) vs. placebo + CT (536)	8 mg/kg, every two weeks	CTCAE	26 and 11%	Ramucirumab increased the risk of \geq G3 HTN	(46)
Grothey <i>et al.</i> , 2013	Prospective	III	NR	1,052	Regorafenib (505) vs. placebo (255)	160 mg qd	CTCAE	28 and 7%	Regorafenib increased the risk of \geq G3 HTN	(47)
Galfrascoli <i>et al.</i> , 2011	Meta-analysis	NR	NR	3,385	Bevacizumab	NR	NR	NR	Bevacizumab increased the risk of \geq G3 HTN	(53)
Xu <i>et al.</i> , 2017	Prospective study	Ib-II	NR	113	Fruquintinib (47) vs. placebo (24)	5 mg for 3 weeks on, 1 week off	CTCAE	NR and 29.8%	Fruquintinib increased the risk of \geq G3 HTN	(48)
Scartozzi <i>et al.</i> , 2009	Retrospective study	NR	First line	39	Bevacizumab + CT	5 mg/kg every 2 weeks	CTCAE	20% ^b	Bevacizumab-induced HTN may represent an interesting prognostic factor for clinical outcome	(49)
Nakaya <i>et al.</i> , 2016	Retrospective study	NR	First and second line	315	Bevacizumab	5 mg/kg in first-line and 10 mg/kg in second-line, every 2 weeks	CTCAE	NR	HTN may be a predictive marker for the efficacy	(14)

Table V. Continued.

Authors, year	Study type	Phase	Treatment lines	Sample size	Drug	Dose and frequency	Definition of HTN	Incidence of HTN and ≥G3 HTN	Main finding	Refs.
Tahover <i>et al</i> , 2015	Cohort study		NR	308	Bevacizumab + CT	2.5 mg/kg/week every 2 or 3 weeks	CTCAE	75.3 and 29.2%	HTN is a harbinger of longer overall survival	(54)
Tahover <i>et al</i> , 2013	Retrospective study		NR	181	Bevacizumab + CT	2.5 mg/kg/Week, every 2 or 3 weeks	CTCAE	44.75% ^b	HTN may represent a biomarker for clinical benefit	(50)

^aIncidence of ≥G3 hypertension in elderly patients (≥75 years) vs in young patients (<75 years); bgrades 2-3 hypertension. HTN, hypertension; G3, grade 3; NR, not reported; CT, chemotherapy, qd, once daily.

Table VI. Association between antiangiogenic drugs and hypertension in hepatocellular carcinoma.

Authors, year	Study type	Phase	Treatment lines	Sample size	Drug	Dose and frequency	Incidence of HTN	Main finding	Refs.
Abou <i>et al</i> , 2018	Prospective study	III	Second or greater	707	Cabozantinib (470) vs. placebo (237)	60 mg qd	29 and 16%	Cabozantinib increased the risk of ≥G3 HTN	(63)
Zhu <i>et al</i> , 2019	Prospective study	III	NR	292	Ramucirumab (197) vs. placebo (95)	8 mg/kg every 2 weeks	25 and 13%	Ramucirumab increased the risk of ≥G3 HTN	(66)
Zhu <i>et al</i> , 2015	Prospective study	III	Second line	562	Ramucirumab (283) vs. placebo (282)	8 mg/kg every 2 weeks	21 and 13%	Ramucirumab as second-line treatment increased the risk of ≥G3 HTN	(65)
Bruix <i>et al</i> , 2017	Prospective study	III	Second line	573	Regorafenib (390) vs. placebo (194)	160 mg qd	23 and 13%	Regorafenib increased the risk of ≥G3 HTN in patients	(64)
Akutsu <i>et al</i> , 2015	Retrospective study		NR	38	Sorafenib	800 or 400 mg/day	58% ^a	HTN may be predictor of anticancer efficacy	(67)

^aPatients who developed grade 2 or higher hypertension within 2 weeks. HTN, hypertension; G3, grade 3; NR, not reported. qd, once daily.

Table VII. Association between antiangiogenic drugs and hypertension in breast cancer.

Authors, year	Study type	Phase	Treatment line	Sample size	Drug	Dose and frequency	Incidence of HTN (%)	Main finding	Refs.
Bear <i>et al.</i> , 2012	Prospective study	NR	NR	1,206	Bevacizumab + CT (595) vs. CT (596)	15 mg/kg, every 3 weeks	NR and 3%	Bevacizumab increased the risk of \geq G3 HTN	(72)
Cortes <i>et al.</i> , 2012	Meta-analysis	III	NR	3,792	Bevacizumab	2.5 or 5 mg/kg per week	NR	Bevacizumab increased the risk of \geq G3 HTN	(77)
Miles <i>et al.</i> , 2010	Prospective study	III	NR	736	Bevacizumab + CT (495) vs. CT (241)	7.5 or 15 mg/kg every 3 weeks	0.8 and 4.5% ^a	Bevacizumab increased the risk of \geq G3 HTN	(73)
Robert <i>et al.</i> , 2011	Prospective study	III	NR	1,237	Bevacizumab + CT (824) vs. placebo + CT (423)	15 mg/kg every 3 weeks	NR and 9.83%	Bevacizumab increased the risk of \geq G3 HTN	(74)
Fan <i>et al.</i> , 2014	Prospective study	NR	NR	80	Apatinib	750 or 500 mg qd	66.3 and 17.5%	Hypertension was associated with improved clinical outcomes	(75)
Schneider <i>et al.</i> , 2008	Retrospective study	III	NR	363	Bevacizumab	NR	NR	Patients with \geq G3 HTN had a superior median overall survival time	(76)

^aIncidence of \geq G3 hypertension in 7.5 mg/kg group and 15 mg/kg group. HTN, hypertension; G3, grade 3; NR, not reported; CT, chemotherapy. qd, once daily.

incidence of severe hypertension was the highest in hepatocellular carcinoma (13.48%) and the lowest in breast cancer (7.1%). Second, there was no significant difference in the incidence of hypertension between monoclonal antibodies and small molecule TKI treatments. Of note, the use of several novel TKIs has been associated with a higher incidence of severe hypertension, such as axitinib in renal cell cancer (18%) (19), fruquintinib in colorectal cancer (29.8%) (48), apatinib in breast cancer (17.5%) (75), and combination of bevacizumab with erlotinib in lung cancer (23%) (34). However, this effect was not observed in the combined antiangiogenic immunotherapy arm (79). In addition, hypertension as an adverse event was more common in patients receiving high doses (41), however, the effect of frequency of administration on the occurrence of hypertension remains unclear. Third, hypertension was more likely to occur in patients younger than 75 years old (43,56,57), those who have not previously used bevacizumab (60,61), and female patients (41). Fourth, the effect of baseline blood pressure levels on the development of hypertension is controversial. Pivot *et al.* (78) reported that there was no clear correlation between baseline hypertension and its development during study treatment. By contrast, Yang *et al.* (80) found that a history of hypertension was an independent risk factor for predicting hypertension during the treatment period. Fifth, discontinuation or death caused by hypertension was rare. Nevertheless, hypertension was a risk factor for acute and chronic cardiovascular diseases and ischemic stroke, with the grade of hypertension associated with mortality (77,81). Finally, early development of significant hypertension may be a biomarker associated with greater efficacy of antiangiogenic therapy and improved survival (14,49,50).

Large doses of antiangiogenic agents are generally associated with greater inhibitory effects on VEGF. We speculate that higher sensitivity to angiogenesis inhibitors may be an explanation, due to different levels of VEGF expression. Patients with RCC have increased levels of VEGF and VEGFR expression (82), which is accompanied by higher rates of hypertension development, compared with hepatocellular carcinoma patients treated with sorafenib (83). Frey *et al.* (84) have shown that bevacizumab-induced hypertension is related to genetic variation in WNK lysine deficient protein kinase 1, kallikrein B1 and G protein-coupled receptor kinase 4. The performance of sunitinib in patients with non-small cell lung cancer (85), bevacizumab in Chinese patients with locally progressed GC (86), as well as sorafenib (87) and sunitinib (88) in patients with breast cancer, confirms our hypothesis: These drugs did not increase the risk of serious hypertension, but at the same time, they did not improve survival.

As an adverse event, hypertension caused by antiangiogenic drugs should be monitored regularly by physicians. There is a role for home or ambulatory blood pressure monitoring, which can increase the sensitivity of diagnosing hypertension (89). Nevertheless, blood pressure monitoring in the clinic is recommended for the first cycle of therapy (90). When blood pressure remains $<140/90$ mmHg, lifestyle intervention is recommended, which includes lower salt intake, reduced alcohol consumption, normalization of the body mass index, no cigarette smoking and increased physical activity (91). Antihypertensive therapy should be initiated when blood pressure is $>140/90$ mmHg or 20 mmHg greater than the baseline blood pressure (90). The

association between antihypertensive drugs and cancer is a matter of large debate in the last several years. At present, renin inhibitors, including ACEIs and angiotensin receptor blockers, are the first-line agents preferred for antiangiogenic therapy, since they can improve remodeling by reducing left ventricular afterload and by direct inhibition of angiotensin II type 1 receptor-mediated hypertrophy and fibrosis (13). After the end of antiangiogenic drug treatment, blood pressure should be regularly monitored, and antihypertensive treatment should be discontinued if it normalizes.

On the other hand, the presence of hypertension has been reported as a positive prognostic biomarker of improved survival in patients receiving antiangiogenic therapy. However, the underlying mechanisms, the timing and value of blood pressure that best predicts survival needs to be elucidated. Previous studies have shown that significant hypertension [$\geq G2$ (22,23) or $\geq G3$ (76)] and early occurrence of hypertension [in the first two (67), four (15) or six weeks of treatment initiation (21)] may be associated with improved survival. However, it is unclear whether patients who do not develop significant hypertension in the early stage need alterations in the medication regimen (15).

9. Conclusion

In conclusion, the use of antiangiogenic drugs is associated with an increased risk of hypertension in most types of solid cancer. Early development of significant hypertension may be a potential biomarker of improved survival. Prospective studies are needed to support these findings.

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Authors' contributions

GT, PS and LZ designed and arranged the manuscript. MD and RW wrote the article. DZ, ZZ and JZ found and analyzed the references in Medline, and participated in writing the article. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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