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ORIGINAL ARTICLE

Incidence and risk of hypertension with pazopanib in patients with cancer: a meta-analysis

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Abstracts

Purposes To gain a better understanding of the overall incidence and risk of hypertension in cancer patients who receive pazopanib and to compare the differences in incidence among sorafenib, sunitinib, and pazopanib.

Methods Several databases were searched, including PubMed, Embase, and Cochrane databases. Eligible studies were phase II and III prospective clinical trials of patients with cancer assigned single drug pazopanib 800 mg/day with data on hypertension available. Overall incidence rates, relative risk (RR), and 95 % confidence intervals (CI) were calculated employing fixed or random effects models depending on the heterogeneity of the included trials.

Results A total of 1,651 patients with a variety of solid tumors from 13 clinical trials were included for the meta-analysis. The overall incidences of all-grade and high-grade hypertension in cancer patients were 35.9 % (95 % CI 31.5–40.6 %) and 6.5 % (95 % CI 5.2–8.0 %), respectively. The use of pazopanib was associated with an increased risk of developing all-grade (RR 4.97, 95 % CI 3.38–7.30, $p < 0.001$) and high-grade hypertension (RR 2.87, 95 % CI 1.16–7.12, $p = 0.023$). Additionally, there was no significant difference in the incidence of all-grade (RR 1.21, 95 % CI 0.96–1.53, $p = 0.11$) and high-grade hypertension (RR 1.29, 95 % CI 0.80–2.07, $p = 0.30$) between RCC and non-RCC patients. Interestingly, the risk of all-grade hypertension with pazopanib was substantially higher than sorafenib (RR 1.99; 95 % CI 1.73–2.29, $p = 0.00$) and sunitinib (RR 2.20; 95 % CI 1.92–2.52, $p = 0.00$), while the risk of pazopanib-induced high-grade hypertension was similar to sorafenib (RR 0.98; 95 % CI 0.75–1.30, $p = 0.90$) and sunitinib (RR 0.81; 95 % CI 0.62–1.06, $p = 0.12$).

Conclusions The use of pazopanib is associated with a significantly increased risk of developing hypertension. Close monitoring and appropriate managements are recommended during the therapy. Future studies are still needed to investigate the risk reduction and possible use of pazopanib in selected patients.

Keywords Pazopanib · Hypertension · Tyrosine kinase inhibit · Meta-analysis

Introduction

Although cytotoxic chemotherapy has still been the cornerstone of cancer treatment, advances in understanding of tumor biology and the molecular pathways involved in cancer cells proliferation have ushered the age of molecularly targeted agents for cancer treatment, with the promise of improved efficacy and a more favorable toxicity profiles [1, 2]. Vascular endothelial growth factor (VEGF) plays an important role in tumor growth and metastasis by promoting angiogenesis, and the blockade of its signaling pathway has become a major approach for current cancer treatment [3].

Pazopanib (GW786034, Votrient; GlaxoSmithKline, Brentford, UK), an oral angiogenesis inhibitor targeting VEGF-1, VEGF-2, and VEGF-3 receptors, and PDGF-α

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and PDGF-β receptors, and c-kit, is recently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment for advanced renal cell carcinoma (RCC) at the dose of 800 mg given orally daily [4–6]. In the pivotal phase III study for metastatic renal cell carcinoma (mRCC), pazopanib led to a clinically relevant and statistically significant longer progression-free survival (PFS) time of 5 months versus placebo [7]. Another large phase III randomized controlled trials for soft tissue sarcoma also demonstrated that pazopanib significantly improved PFS compared with placebo (4.6 versus 1.6 months, respectively) [8]. Additionally, pazopanib is currently being assessed for activity among other types of tumors in more than 100 registered active clinical trials enrolling thousands of patients [9]. Therefore, an increase in the use of pazopanib is expected in the near future.

As with other VEGFR-TKIs (sorafenib and sunitinib), pazopanib is associated with substantial side effects including diarrhea, fatigue, nausea, vomiting, anorexia, and headache [10–15]. Also, two previous meta-analyses demonstrated that the use of sorafenib or sunitinib has a significant risk of developing hypertension compared with control, and the incidences of all-grade and high-grade hypertension were observed in 23.4 and 5.7 % of patients treated with sorafenib and in 21.6 and 6.8 % among patients treated with sunitinib [16, 17]. As pazopanib shares a similar spectrum of target receptors with sorafenib and sunitinib, including VEGFR, PDGFR, and c-kit tyrosine kinases [18], and specific receptor inhibition may play a critical role in the pathogenesis of hypertension, thus one could anticipate pazopanib to cause this adverse event as well. Indeed, hypertension is a major side effect that has been noted in many clinical trials, with its incidences ranging from 15 to 46 % [19, 20]. It is because poorly controlled hypertension may lead to serious cardiovascular events, dose reduction, and life-threatening consequences, the monitoring and management of hypertension are of particular importance [21]. In addition, exploring the differences in the occurrence of hypertension among sorafenib, sunitinib, and pazopanib may offer additional insights into the understanding of underlying mechanisms, risk factors, and potential management strategies. Therefore, we conduct this meta-analysis of all published trials to determine the incidence and relative risk of hypertension among patients administered pazopanib.

Methods

Search strategy

We searched the PubMed (data from 1966 to May 2012), Embase (data from 1980 to May 2012), and the Cochrane Library electronic databases. Keywords included in the search were 'pazopanib,' 'GW786034,' 'cancer,' 'randomized,' and 'hypertension,' The search was restricted to clinical trials and articles published in English. Abstracts presented at the annual meetings of the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) (from 2001 to 2012) were also searched manually using the same keywords. Additionally, we searched the clinical trial registration website (http://www.ClinicalTrials.gov) to obtain information on the registered randomized controlled trials (RCTs). We also reviewed the reference lists of the original and review articles to identify relevant studies.

Study selection

Two investigators independently assessed the eligibility of the articles and abstracts identified by the search, and discrepancies were resolved by consensus. Pazopanib had been approved for use in patients with advanced RCC as a single agent at 800 mg orally once daily [4, 5]. To ensure clinical significance, we assessed the risk of hypertension with pazopanib at this dose level. Thus, phase I trials were excluded from analyses due to multiple dose level and limited sample sizes. The clinical trials that met the following criteria were selected for the final analysis: (1) prospective phase II and III clinical trails in cancer patients; (2) participants assigned to treatment with only pazopanib at a dosage of 800 mg orally once daily; and (3) events or event rate and sample size available for hypertension. If multiple publications of the same trial were retrieved or if there was a case mix between publications, only the most recent publication (and the most informative) was included.

Clinical end points

Hypertension was extracted from the safety profile in each trial. These clinical end points were recorded according to versions III of the Common Terminology Criteria for Adverse Events (CTCAE) of National Cancer Institute (http://ctep.cancer.gov/reporting/ctc_archive.html) [22]. The CTC version 3.0 describes the grading of hypertension as follows: grade I, asymptomatic, transient (<24 h) increase of blood pressure by >20 mmHg (diastolic) or to >150/100 mmHg if previously within normal limit (WNL), intervention may not indicated; grade II, recurrent or persistent (>24 h) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 mmHg if previously WNL, monotherapy may be indicated; grade III, requiring more than one drug or more intensive therapy than previously; and grade IV, hypertensive crisis. We included all incidences of hypertension of grade 1 or above in our analysis.

Data analysis

The analysis was undertaken on an intention-to-treat basis: patients were analyzed according to treatment allocated, irrespective of whether they received that treatment. The data of the number of patients with all grades and high grades (grade 3 and grade 4) of hypertension and the number of patients receiving pazopanib were extracted from the adverse events outcomes. For each study, we derived the proportion and 95 % confidence interval (CI) of patients with hypertension. For studies with a control group in the same trial, we also calculated and compared the relative risk (RR) of hypertension. For one study that reported zero events in the control arm, we applied the classic half-integer correction to calculate the RR and variance [23]. Between-study heterogeneity was estimated using the χ^2-based Q statistic [24]. Heterogeneity was considered statistically significant when $P_{\text{heterogeneity}} < 0.05$ or $I^2 > 50$ %. If heterogeneity existed, data were analyzed using a random effects model. In the absence of heterogeneity, a fixed effects model was used. To calculate the pooled incidence, an inverse variance statistical method was used. A statistical test with a p value less than 0.05 was considered significant. The presence of publication bias was evaluated by using the Begg's and Egger's tests [25, 26]. All statistical analyses were performed by using Stata version 12.0 software (Stata Corporation, College Station, Texas, USA) and Open Meta-Analyst software version 4.16.12 (Tufts University, URL http://tuftscaes.org/open_meta/).

Results

Search results

Our search yielded a total of 303 articles on pazopanib from the literature. After reviewing each publication, thirteen original studies met our inclusion criteria. From the abstracts published during recent American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) annual meetings (2004–2012), 10 abstracts related to pazopanib were also identified. After reviewing each abstract, none of these trials was included in our meta-analysis. As a result, a total of 13 trials were finally available for the meta-analysis (Fig. 1) [7, 8, 19, 20, 27–35], encompassing four randomized controlled trials [7, 8, 32, 34] and nine phase II single-arm trials [19, 20, 27–31, 33, 35]. A total of 1,651 patients were included, and baseline characteristics of these eligible trials are given in Table 1. For calculation of the RRs, four trials were pooled; 628 patients were assigned to the drug group (pazopanib 800 mg/day); and 365 patients were assigned to the control or placebo groups (Table 1). Hypertension was not described as a preexisting condition in any of the trials. The underlying metastatic malignancies include RCC [7, 27], STS [8, 28], NSCLC [29], thyroid cancer [20], ovarian cancer [30], glioblastoma [31], cervical cancer [32], breast cancer [19], nasopharyngeal carcinoma [33], prostate cancer [34], and urothelial cancer [35].

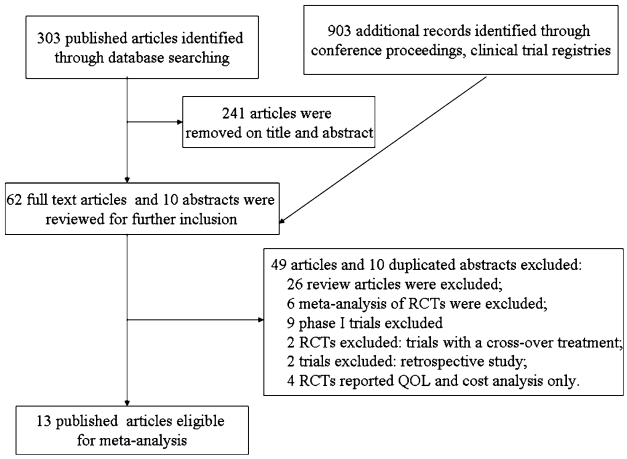

Fig. 1 Selection process for the trials included in the meta-analysis

Incidence of all-grade hypertension

A total of 1212 patients from 11 trials were included for this analysis [7, 8, 19, 20, 27–32, 34]. The majority of these patients had either RCC or STS. The incidence of all-grade hypertension ranged from 15.3 to 46.2 %; the lowest incidence was noted in a phase II single-arm trial among patients with MBC [19], and the highest incidence was observed in patients with metastatic thyroid cancer [20]. Our meta-analysis revealed a significant heterogeneity among included studies ($I^2 = 55$ %, $p = 0.013$), and the calculated summary incidence of all-grade hypertension among patients receiving pazopanib was 35.9 % (95 % CI 31.5–40.6 %, Fig. 2) using a random effects model.

Incidence of high-grade hypertension

High-grade (grade 3 or 4) hypertension was associated with significant morbidity and might result in dose reduction or discontinuation of pazopanib. All of the 13 trials reported the incidence of high-grade hypertension data ranging from 1.4 to 16.7 %. The highest incidence was observed in a phase II trial conducted by Ward et al. [34] in patients with castrate-sensitive prostate cancer, and the lowest incidence was observed in patients with NSCLC, glioblastoma, and cervical cancer [29, 31, 32]. The calculated summary incidence of high-grade hypertension among 1286 patients receiving pazopanib was 6.5 % (95 % CI 5.2–8.0 %,

Table 1 The characteristics of trials included in the meta-analysis

Study	Phase	Underlying malignancy	Treatment arms	Patients number	Median age (years)	Female (%)	Median PFS (months)	Median OS (months)	Number of high-grade hypertension events	CTC version
Hutson et al. [27]	II	Metastatic RCC	Pazopanib 800 mmg/day	225	59.8	31	45 (weeks)	NR	20	3.0
Sleijfer et al. [28]	II	Advanced STS	Pazopanib 800 mmg/day	142	51.4	50	NR	NR	11	3.0
Altorki et al. [29]	II	NSCLC	Pazopanib 800 mmg/day	35	64	63	NR	NR	0	3.0
Bible et al. [20]	II	Metastatic thyroid cancer	Pazopanib 800 mmg/day	39	63	18	NR	NR	1	3.0
Friedlander et al. [30]	II	Recurrent ovarian cancer	Pazopanib 800 mmg/day	36	59.9	36	NR	NR	1	3.0
Iwamoto et al. [31]	II	Recurrent glioblastoma	Pazopanib 800 mmg/day	35	53	37	12 (weeks)	35 (weeks)	0	3.0
Monk et al. [32]	II	Advanced cervical cancer	Pazopanib 800 mmg/day	74	49.5	NR	18.1 (weeks)	50.7 (weeks)	0	3.0
			Lapatinib	78	49	NR	17.1 (weeks)	39.1 (weeks)	0	
Sternberg [7]	III	Advanced RCC	Pazopanib 800 mmg/day	290	59	32	9.2	NR	13	3.0
			Placebo	145	60	25	4.2	NR	1	
Taylor et al. [19]	II	Metastatic breast cancer	Pazopanib 800 mmg/day	72	56	100	5.3	NR	3	3.0
Lim et al. [33]	II	Nasopharyngeal carcinoma	Pazopanib 800 mmg/day	33	50	10	4.4	10.8	1	3.0
Ward et al. [34]	II	Castrate-sensitive prostate cancer	Pazopanib 800 mmg/day	18	NR	NR	NR	NR	3	3.0
			Observation	19	NR	NR	NR	NR	0	
Van Der Graaf et al. [8]	III	Metastatic STS	Pazopanib 800 mmg/day	246	56.7	60	4.6	12.5	16	3.0
			Placebo	123	51.9	56	1.6	10.7	4	
Necchi et al. [35]	II	Advanced urothelial cancer	Pazopanib 800 mmg/day	41	NR	NR	NR	NR	3	3.0

RCC renal cell carcinoma, *NSCLC* non-small-cell lung cancer, *STS* soft tissue sarcoma, *NR* not reported

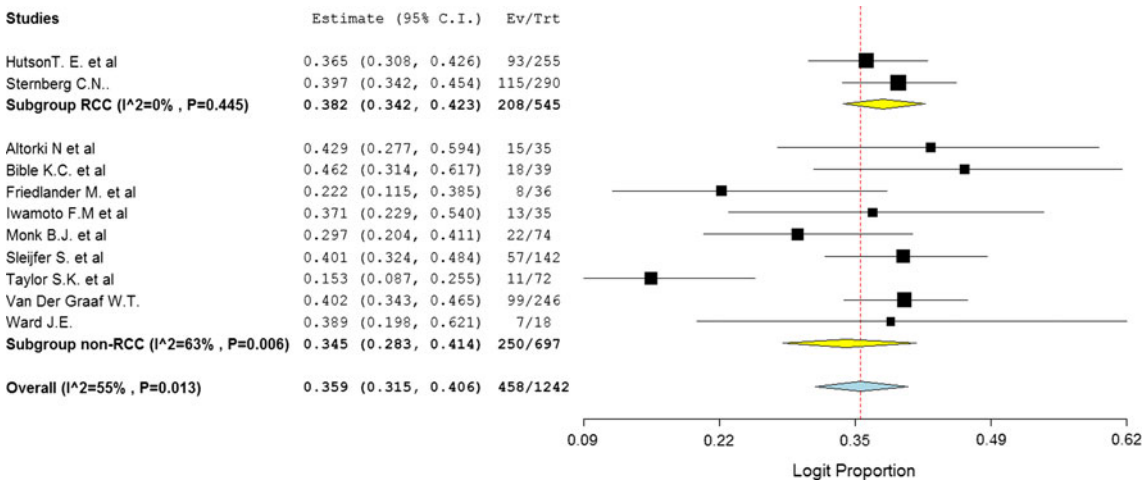

Fig. 2 Forest plot for meta-analysis of incidence of all-grade hypertension in cancer patients assigned pazopanib

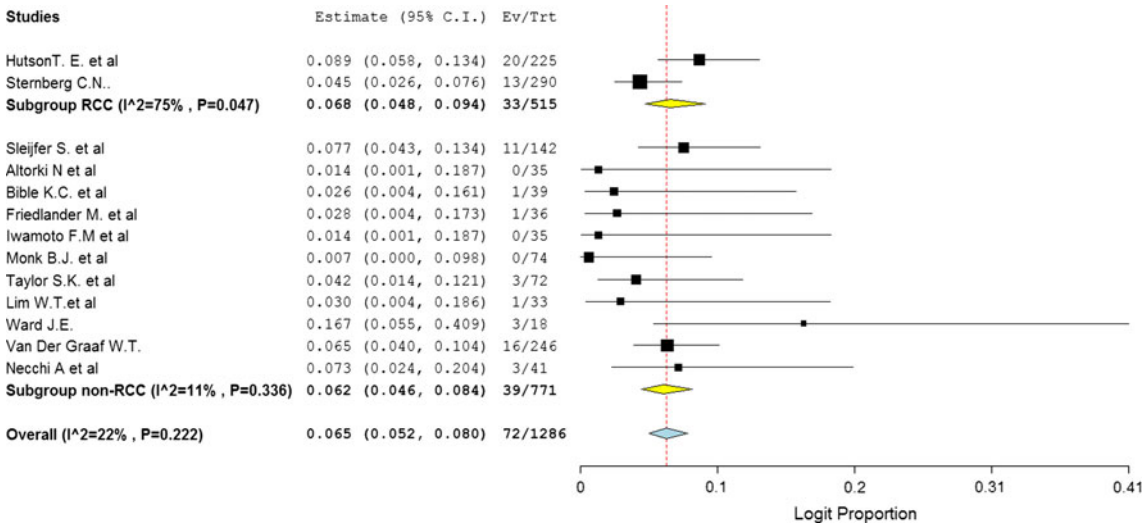

Fig. 3 Forest plot for meta-analysis of incidence of high-grade hypertension in cancer patients assigned pazopanib

Fig. 3) using the fixed effects model ($I^2 = 22$ %, $p = 0.222$).

Incidence of hypertension in patients with RCC versus non-RCC solid tumors

In order to explore the relationship between pazopanib-associated hypertension and tumor type, we further analyzed the incidence of hypertension in patients with RCC and non-RCCs. The overall incidences of all-grade and high-grade hypertension were 38.2 and 6.8 % among RCC patients, while the pooled incidences of all-grade and high-grade hypertension were 34.5 and 6.2 % in non-RCC patients, respectively. Although the incidences of all-grade and high-grade hypertension in RCC were higher than those in non-RCCs, no significant difference was detected between RCC and non-RCCs in terms of all-grade (RR 1.21, 95 % CI 0.96–1.53, $p = 0.11$) and high-grade hypertension (RR 1.29, 95 % CI 0.80–2.07, $p = 0.30$).

Relative risk of hypertension

With a view to investigate the specific contribution of pazopanib to the development of hypertension and exclude the influence of confounding factors such as underlying malignancy, and other therapeutic interventions, we then determined the relative risk (RR) of pazopanib-induced hypertension. The pooled RR showed that pazopanib treatment significantly increased the risk of developing all-grade hypertension in cancer patients with a RR of 4.97 (95 % CI 3.38–7.30, $p < 0.001$, Fig. 4) using a fixed effects model ($I^2 = 14$ %, $p = 0.325$). Similar results for

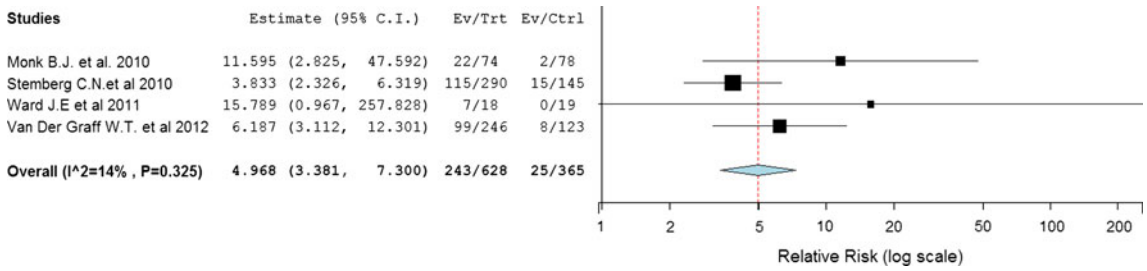

Fig. 4 Relative risk of pazopanib-associated all-grade hypertension versus control from randomized controlled trials of patients with cancer

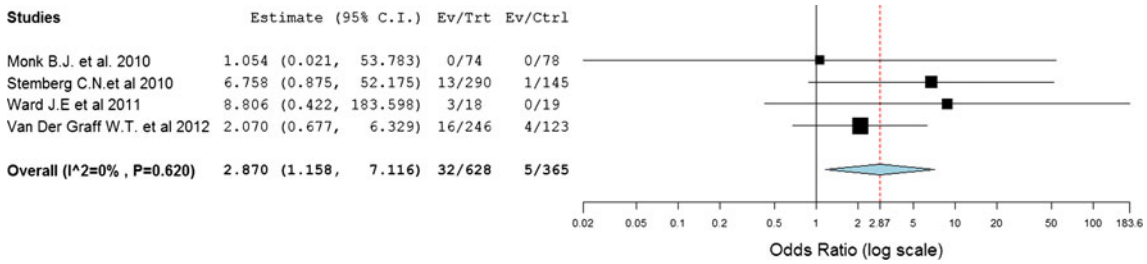

Fig. 5 Relative risk of pazopanib-associated high-grade hypertension versus control from randomized controlled trials of patients with cancer

high-grade hypertension were also observed in cancer patients receiving pazopanib (RR 2.87, 95 % CI 1.16–7.12, $p = 0.023$, Fig. 5) using a fixed effects model ($I^2 = 0$ %, $p = 0.62$).

Differences in hypertension incidence among various VEGFR-TKIs approved for RCC treatment

We further explored the differences in the incidence of hypertension among various VEGFR-TKIs. The risk of all-grade hypertension with pazopanib was substantially higher when compared to sorafenib (RR 1.99; 95 % CI 1.73–2.29, $p = 0.00$) and sunitinib (RR 2.20; 95 % CI 1.92–2.52, $p = 0.00$), while the risk of high-grade hypertension with pazopanib was similar to sorafenib (RR 0.98; 95 % CI 0.75–1.30, $p = 0.90$) and sunitinib (RR 0.81; 95 % CI 0.62–1.06, $p = 0.12$) (Table 2).

Publication bias

No evidence of publication bias was detected for the RR of all-grade and high-grade hypertension in this study by either Begg's or Egger's test (RR of all-grade hypertension: Begg's test $p = 0.296$; Egger's test $p = 0.135$).

Discussion

Hypertension associated with angiogenesis inhibitors is a common adverse event observed in clinical trials. In addition to pazopanib, several other angiogenesis inhibitors, such as sorafenib, sunitinib, and bevacizumab, have been also associated with an increased risk of developing hypertension [16, 17, 36]. However, to our knowledge, this is the first meta-analysis to investigate the overall incidence

Table 2 Comparison of the risk of hypertension between pazopanib with sorafenib and sunitinib

Risk subset	Incidence (sample size) Pazopanib	Incidence (sample size) Sorafenib[a]	Risk ratio (95 % CI)	*p* value
All-grade	35.5 % (1,212)	23.4 % (3,363)	1.99 (95 % CI 1.73–2.29)	0.00
High-grade	6.5 % (1,286)	5.7 % (3,567)	0.98 (95 % CI 0.75–1.30)	0.90
	Pazopanib	Sunitinib[a]		
All-grade	35.5 % (1,212)	21.6 % (4,609)	2.20 (95 % CI 1.92–2.52)	0.00
High-grade	6.5 % (1,286)	6.8 % (4,407)	0.81 (95 % CI 0.62–1.06)	0.12

[a] The incidences for sorafenib- and sunitinib-associated hypertension are derived from previous systematic reviews [16, 17]

and risk of hypertension associated with pazopanib in cancer patients and to compare the differences in the incidences among VEGFR-TKIs. As with other angiogenesis inhibitors, the mechanisms of pazopanib-induced hypertension may be directly related to its inhibitory effect on VEGF receptor, possible mechanisms include impaired angiogenesis leading to a decrease in the density of microvessels, endothelial dysfunction associates with a decrease in nitric-oxide production and an increase in oxidative stress, and changes in neurohormonal factors or the rennin–angiotension–aldosterone system [17, 37]. In addition, Veronese M. L. et al. [38] did a study and found that neurohormonal factors had little role in the sorafenib-induced hypertension. However, as yet, there is limited data on the possible mechanism of pazopanib-associated hypertension. More studies focusing on this issue are still required.

Our meta-analysis results demonstrate that pazopanib monotherapy is associated with an increased risk of developing hypertension. The overall incidence of all-grade hypertension was 35.9 % (95 % CI 31.5–40.6 %) with a RR of 4.97 (95 % CI 3.38–7.30, $p < 0.001$). And the risk of developing high-grade hypertension also increases (RR 2.87, 95 % CI 1.16–7.12, $p = 0.023$), though the overall incidence of high-grade hypertension is low (6.5 %; 95 % CI 5.2–8.0 %). Additionally, the risk of developing hypertension may substantially vary with tumor types; thus, we perform a sub-group analysis. Although our results show that pooled all-grade and high-grade incidences of hypertension in patients with RCC seem higher than non-RCC patients, no significant difference is detected between RCC and non-RCC. A possible explanation for this finding is that an increase in blood pressure and hypertension induced by pazopanib is so prominent that the risk associated with RCC is not evident in this setting. This notion is supported by the high incidence of all-grade hypertension with pazopanib noted in this study. Moreover, pazopanib is mainly metabolized by the liver [10], and renal dysfunction associated with RCC might not affect the concentration of pazopanib in the blood in a substantial way.

We further explore the difference in the incidence of hypertension among pazopanib, sorafenib, and sunitinib and find that the incidence of all-grade hypertension associated with pazopanib is higher than that of sorafenib and sunitinib, while the incidence of high-grade hypertension associated with pazopanib is comparable to that of sorafenib and sunitinib. This finding could be a result of different pathogeneses of these malignancies, different spectrum of patient comorbidities, different solid tumors, or a result of the smaller sample size of non-RCC cohort. Alternatively, differences in the incidence of hypertension among various VEGFR-TKIs may stem from the different pharmacodynamic effects. For instance, pazopanib has a greater inhibitory effect on VEGFR-2 as compared to sorafenib ($IC_{50} = 0.030$ vs. 0.09 μmol/L, respectively) based on cell-free biochemical analyses of IC_{50} [18, 35]. In contrast, its ability to inhibit PDGFR-β is inferior to sorafenib (0.084 vs. 0.057 μmol/L) [18, 35]. Interestingly, it has been described that angiogenesis inhibitor-induced hypertension may be associated with improved outcomes. A clinical study conducted by Ravaud et al. [39] demonstrates that patients with bevacizumab-induced hypertension had an increase in PFS and OS. The same effect may be possible for pazopanib; however, there are no data to prove this concept so far.

Adequate and aggressive management of moderate hypertension could be essential for many patients, because hypertension is an independent risk factor for renal and cardiovascular events [21, 40]. However, the treatment for pazopanib-associated hypertension is still under debate. According to the manufacturer package insert for pazopanib [4], blood pressure should be well-controlled prior to initiating pazopanib. All patients should be monitored for hypertension and treated as needed with antihypertensive therapy. In cases of severe or persistent hypertension despite the initiation of antihypertensive treatment, dose reduction or interruption may be necessary. If patients with high blood pressure cannot be controlled, pazopanib should not be restarted. In most patients, hypertension can be controlled with standard antihypertensive medications. However, the biological effect of these antihypertensive medications on angiogenesis and its implications should be considered. Both enalapril (an angiotensin-converting enzyme [ACE] inhibitor) and candesartan (an angiotensin receptor blocker) can inhibit myocardial angiogenesis induced by EVGF [41]. However, nifedipine (a calcium channel blocker) has been shown to induce VEGF secretion [42]. Diuretics also have been used successfully to manage increases in blood pressure arising from cancer treatment; however, thiazide-type diuretics should be used cautiously, particularly in patients prone to dehydration or hypercalcemia [43]. Thus, the possibility exists that some antihypertensive medications are more effective in treating anti-VEGF-associated hypertension and have less toxic effects when used in conjunction with pazopanib.

Drug–drug interactions are also important issues. As with other VEGFR-TKIs, pazopanib undergoes some metabolism by the cytochrome P450 enzyme system, mainly by CYP3A4, and therefore, it is a candidate for drug–drug interactions involving this isozyme. For that reason, until more formal studies are undertaken, it should be used cautiously with antihypertensive compounds, such as verapamil and diltiazem that are inhibitors of CYP3A4. Dihydropyridine calcium channel blockers do not inhibit CYP3A4, although they are substrates for CYP3A4; thus, they would be preferred agents if a calcium channel

blocker is selected for antihypertensive therapy. Alternatively, compounds that improve microcirculatory structure and function, such as ACE inhibitors and angiotensin receptor blockers, can be considered for empiric use in patients with angiogenesis inhibitor-related hypertension [44].

This meta-analysis has some limitations. First, the prevalence of baseline hypertension is not described in the included trials, which may have led to an overestimation of the incidence of pazopanib-associated hypertension. However, we have minimized the likelihood of bias by calculating relative risk using randomized controlled clinical trials, with direct comparison with and without pazopanib. Additionally, these included trials may have underestimated the incidence of pazopanib-associated hypertension because of the imperfection of the CTCAE version 2 or 3. In both versions, patients were considered hypertensive only if diastolic pressure increased >20 mmHg or blood pressure was >150/100 mmHg. These grading criteria likely underestimate the incidence of hypertension according to the standard criteria for the diagnosis of hypertension (140/90 mmHg). Secondly, these studies are conducted at various international institutions by different investigators and may have potential bias in reporting the types of adverse events. In addition, only patients with adequate major organ function are included in these trials, and therefore, the results may not reflect the general patient population in the community or patients with organ dysfunction. Thirdly, it should be noted that our meta-analysis is not a standard Cochrane meta-analysis, and the statistical methods for incidence rate meta-analysis, such as the common method of adding a correction factor to handle zeroes, are still needed to be improved [45], though more and more such meta-analyses have been performed in recent years. Finally, it is not an individual patient data analysis, and meta-analyses based on published data tend to overestimate treatment effects compared with individual patient data analyses. In addition, it precludes a more comprehensive analysis such as adjusting for baseline factors and other differences that existed between the trials from which the data were pooled.

In conclusion, our study suggests that the use of pazopanib is associated with a significant risk of developing hypertension. As this drug gains greater clinical use, clinicians should be aware of the possibility that any patient treated with pazopanib may develop hypertension, especially those at high risk. Close monitoring and appropriate management are recommended during the therapy. Future studies are still needed to investigate the risk reduction and possible use of pazopanib in selected patients.

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Conflicts of interest All authors declare that they have no potential conflicts of interest.

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