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Risk of treatment-related deaths with vascular endothelial growth factor receptor tyrosine kinase inhibitors: a meta-analysis of 41 randomized controlled trials

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Background: Vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) have widely been used in advanced cancer. However, these drugs may also lead to serious adverse events. The present meta-analysis aimed to determine the overall incidence and risk of deaths due to VEGFR-TKIs with more detailed subgroup analysis.

Materials and methods: PubMed, Web of Science, and Cochrane databases were searched for randomized controlled trials (RCTs) that compared VEGFR-TKIs with non-VEGFR-TKIs in the treatment of solid cancer. Pooled incidence, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using random-effects or fixed-effects models based on the heterogeneity of included trials.

Results: A total of 14,139 participants from 41 RCTs were enrolled. The pooled incidence of death due to VEGFR-TKIs was 1.9% (95% CI: 1.6%–2.3%) with an OR of 1.85 (95% CI: 1.33–2.58; $P<0.01$) when compared with control groups. On subgroup analysis, significantly increased risk of death was found in patients with nonsmall-cell lung cancer (OR: 2.37; 95% CI: 1.19–4.73; $P=0.01$) and colorectal cancer (OR: 2.84; 95% CI: 1.02–7.96; $P=0.05$). Among different VEGFR-TKIs, sorafenib and sunitinib had significant risk of death when compared with control arms, respectively. VEGFR-TKIs in combination with other antineoplastic agents, but not VEGFR-TKI monotherapy, significantly increased the risk of treatment-related deaths. No heterogeneity was noted across all the prespecified subgroups regarding ORs.

Conclusion: The present work pointed out a significantly increased risk of death due to VEGFR-TKIs. Close monitoring should be emphasized in patients receiving these drugs.

Keywords: cancer, tyrosine kinase inhibitors, treatment-related death, meta-analysis

Introduction

Vascular endothelial growth factor (VEGF) plays a critical role in tumor growth, invasion, metastasis, and angiogenesis.[1] It represents an important target in cancer drug development.[2] During the past decades, the use of VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs) and VEGF antibodies has led to considerable improvements in the clinical outcome of patients with various metastatic cancers.[3–6] Until now, several VEGFR-TKIs have been approved by the United States Food and Drug Administration and the European Medicines Agency, including sorafenib, sunitinib, pazopanib, vandetanib, axitinib, regorafenib, and cabozantinib. Their wide clinical use has raised concerns over their associated toxicity.

Despite their different toxicity profile from traditional cytotoxic chemotherapy agents, VEGFR-TKIs could induce life-threatening adverse effects (AEs) including

thromboembolic events, hemorrhage, hypertension, cardiac toxicity, and gastrointestinal perforation.[7] Therefore, drug safety should be given due importance to better manage cancer patients who receive VEGFR-TKIs, especially with respect to the risk of treatment-related deaths (TRDs).

Previous meta-analyses have reported an increased risk of fatal AEs (FAEs) associated with VEGFR-TKIs.[8,9] However, there were several limitations in those studies and many questions remain unanswered. Firstly, the definition of FAEs was ambiguous. FAEs are distinct from TRDs. According to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0,[10] FAEs are defined as deaths that are usually secondary to the use of a pharmaceutical agent, which may or may not be considered related to the medical treatment. In Sivendran et al's study,[8] the researchers simply included all deaths that were not related to cancer progression, regardless of their attribution to the treatment protocol, which might overestimate the contribution of VEGFR-TKIs to fatal events. Secondly, previous studies investigated patients treated with sorafenib, sunitinib, pazopanib, or vandetanib. After these meta-analyses, many studies have been published on the use of these drugs, which may alter the previous conclusions on the risk of death with VEGFR-TKIs.[11–23] In addition, another three VEGFR-TKIs including axitinib, regorafenib, and cabozantinib have also been approved by pharmaceutical agencies. Indeed, FAEs related to these drugs have been sporadically reported in recent clinical trials.[4,24,25] However, their contributions to VEGFR-TKI-related mortality are still undetermined. Finally, a subgroup analysis to explore potential heterogeneity or risk factors remains poorly defined due to the limited number of trials included. Schutz et al's study[9] did not stratify the relative risk of death according to the treatment schedule of VEGFR-TKIs. The influence of other antineoplastic agents in combination with VEGFR-TKIs was not clarified. The risk of death associated with VEGFR-TKIs across different tumor types was also poorly understood. Hence, we conducted this meta-analysis to fully investigate the incidence and odds ratio (OR) of deaths in patients who receive VEGFR-TKIs with a prespecified subgroup analysis.

Materials and methods

Data sources

Citations from PubMed were searched from inception to March 15, 2014 with the following keywords: sorafenib; nexavar; BAY43-9006; sunitinib; sutent; SU11248; pazopanib; votrient; GW786034; vandetanib; caprelsa; ZD6474; axitinib; AG-013736; regorafenib; ABT-869; cabozantinib; XL184; Cometriq; VEGF receptors; clinical trials; and cancer. The search was restricted to human studies published in the English language. Similar strategies were applied to the Web of Science and Cochrane databases to yield additional citations. Abstracts from the American Society of Clinical Oncology and the European Society of Medical Oncology conferences held between January 2008 and March 2014 were also searched for relevant clinical trials. When duplicate or subgroup studies were encountered, the most up-to-date or thorough report of a clinical trial was incorporated. Studies that met the following criteria were included: 1) prospective randomized controlled Phase II or Phase III trials on solid cancer patients; 2) patients randomly assigned to VEGFR-TKIs or control groups; and 3) data available regarding TRDs and the number of patients for the toxicity assessment. When such data were insufficient (ie, there was a lack of attribution of death events), we tried to contact the trial investigators. Phase I and single-arm Phase II trials were excluded for a lack of sufficient controls. Trials comparing VEGFR-TIKs with VEGF antibodies were not included because both drug classes are angiogenesis inhibitors and share a similar toxicity spectrum, which may result in the underestimation of risk with VEGFR-TKIs. Study quality was assessed using the seven-item Jadad scale including randomization, double-blinding, and withdrawals, as previously described.[26]

Data extraction

Two reviewers (Hong SD and Fang WF) independently abstracted data according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[27] Any discrepancies were resolved by consensus. For every study, the following data were collected: name of the first author; year of publication; underlying cancer; number of enrolled patients; median age; treatment line; trial phase; type, dosage, and schedule of VEGFR-TKIs; median treatment duration, median progression-free survival; median overall survival; the number of patients for the toxicity assessment; and FAEs attributed to the treatment protocol and their causes. In cases where several treatment arms received VEGFR-TKIs within a single trial, the VEGFR-TKI-exposed groups were combined together. For each trial, the control groups were defined as patients treated with any drugs other than angiogenesis inhibitors.

Definition of treatment-related deaths

All deaths reported by investigators as "possibly", "probably", or "definitely" related to the treatment protocols were considered TRDs.[28] Some studies had simultaneously reported FAEs and TRDs. In such cases, only TRDs were included. Causes of TRDs were categorized as

follows: hemorrhage; cerebrovascular accidents; renal failure; neutropenia; thromboembolism; pulmonary disorders; cardiopulmonary insufficiency; hepatic failure; gastrointestinal disease; and sudden death. Hemorrhage included any bleeding events, except for central nervous system (CNS) hemorrhage. Thromboembolism included any embolism in organs other than the CNS (ie, myocardial infarction, pulmonary infarction, or deep venous thromboembolism), while cerebrovascular infarction and/or hemorrhage were classified as cerebrovascular accidents. Gastrointestinal disease included perforation, fistula, bowel obstruction, and peritonitis. Pulmonary diseases included pneumonia and interstitial lung disease.

Statistical analysis

All statistical analyses were done using Comprehensive Meta-Analysis software, version 2.0 (Biostat, Inc., Englewood, NJ, USA). To calculate the incidence, the number of TRDs and the number of patients evaluated for toxicities were extracted from the selected articles; the proportion of patients with TRDs and 95% confidence intervals (CIs) were derived for each study. Because many trials reported few TRDs, we calculated the ORs and 95% CIs to assess the risk of death associated with VEGFR-TKIs using the Mantel–Haenszel method. Trials in which patients had no TRDs in both arms were automatically excluded for the calculation of ORs. In case there were no events in either arm, the classic half-integer continuity correction was used to calculate ORs. For the meta-analysis, both fixed-effects and random-effects models were used. Between-study heterogeneity was assessed with the Q statistic and I^2 score. Heterogeneity was deemed significant if $P<0.10$, and in this case, a random-effects model was adopted. Otherwise, results from the fixed-effects model were reported. A prespecified subgroup analysis was also conducted for underlying cancer, VEGFR-TKIs, VEGFR-TKI schedule, study phase, and study quality. To test the stability of the results, a sensitivity analysis was performed by sequentially omitting individual studies. A cumulative meta-analysis was also carried out by sequentially adding trials to the summarized results in the order of publication year to show how the ORs of TRDs shifted over time. Finally, publication bias was assessed with Begg's and Egger's tests. We judged a two-sided $P<0.05$ as statistically significant.

Results

Search results

The literature search yielded 2,995 potentially relevant abstracts. The initial screening excluded 2,602 citations for at least one of the following reasons: Phase I trials; review articles; commentary or letters; not human studies; not in English; case reports; diseases other than cancer; not VEGFR-TKIs; and observational studies. After a careful review of the remaining 393 publications, 41 trials were judged as eligible for the present meta-analysis. These trials comprised 13 Phase II and 28 Phase III studies. The selection process is summarized in Figure 1. Table 1 shows the baseline characteristics of the included trials.

Quality of studies

The 41 randomized controlled trials (RCTs) included were evaluated for study quality using the Jadad scoring system. The overall study quality was fair with a mean Jadad score of 3.5 (range: 2–5). Seven trials with Jadad scores of 2 were categorized as low-quality trials, while the remaining 34 trials were considered to be of high quality. The follow-up time was adequate for each trial. TRDs were assessed according to CTCAE version 2 or 3 in these trials. Death attribution was judged by the study investigators in each trial.

Patients

A total of 14,139 participants from 41 trials were randomized: 7,644 were assigned to receive VEGFR-TKIs and 6,495 were assigned to control groups. The underlying malignancy included nonsmall-cell lung cancer (NSCLC),[21,29–35] colorectal cancer (CRC),[12,14] breast cancer,[16,18,22,24,36–39] renal cell cancer,[5,20,40,41] hepatocellular cancer,[42,43] pancreatic cancer,[17,44] prostate cancer,[11,45] melanoma,[13,46,47] gastrointestinal stromal tumor,[23,25] ovarian cancer,[19] pancreatic neuroendocrine cancer,[6] soft-tissue sarcoma,[3] thyroid cancer,[4,15] small-cell lung cancer,[48] urothelial cancer,[49] and squamous cell carcinoma of the head and neck.[50] In these studies, patients were enrolled under defined eligibility criteria by each unique trial, which included sufficient renal, cardiac, hepatic, and hematologic functions. Most of the patients had baseline Eastern Cooperative Oncology Group Performance status of 0 or 1. Major exclusion criteria for the trials were active brain metastasis, a history of or active hemorrhage, and uncontrolled hypertension. In all trials, patients were randomly allocated to either a control or VEGFR-TKI group, except for three studies which had two VEGFR-TKI treatment groups with different dosages or combinations.[31–33] The evaluated VEGFR-TKIs included sorafenib, sunitinib, pazopanib, vandetanib, cabozantinib, regorafenib, and axitinib.

Incidence and causes of TRDs

A total of 7,527 patients who received VEGFR-TKIs were analyzed for TRDs. There were 108 TRDs among

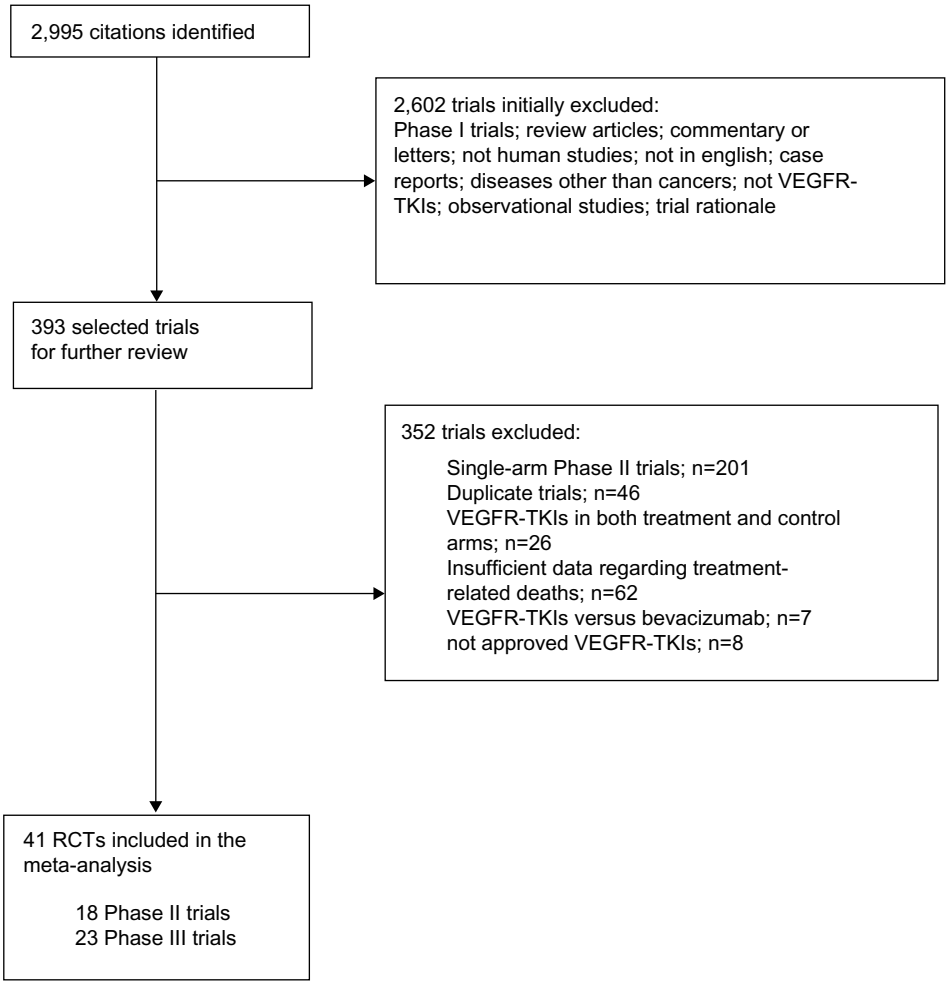

Figure 1 Selection process for the RCTs included in the meta-analysis.
Abbreviations: VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors; n, number; RCTs, randomized controlled trials.

these patients. Using a fixed-effects model (heterogeneity test: Q-value =42.31; P=0.372; I^2=5.5%), the summary incidence of deaths due to VEGFR-TKIs was determined to be 1.9% (95% CI: 1.6%–2.3%) (Figure S1). The highest incidence (4.2%; 95% CI: 2.2%–7.9%) was noted in a Phase III trial in which patients with advanced thyroid cancer were randomly assigned to received placebo or cabozantinib at 140 mg/day.[4] The lowest incidence was observed in 13 trials, which reported no TRDs.[1,2,4,6,8,20,21,23,25,26,28,29,34] For the control group, the incidence of TRDs was 1.1% (95% CI: 0.9%–1.5%). Table 2 demonstrated the overall and stratified analysis. Notably, the incidence of TRDs with VEGFR-TKI combination therapy and monotherapy was 2.0% and 1.6%, respectively. However, this difference was not significant ($P_{difference}$ =0.239).

The most common causes of TRDs included cardiopulmonary insufficiency (11.1%), thromboembolism (8.3%), and gastrointestinal diseases (6.5%). Other causes of death were also summarized in Table S1.

ORs of treatment-related deaths

In order to explore the specific contribution of VEGFR-TKIs to the occurrence of TRDs, we determined the ORs of VEGFR-TKI-related deaths. As shown in Figure 2, a total of 12,313 patients from 32 RCTs were available to calculate the ORs of deaths due to VEGFR-TKIs. Using a fixed-effects model (heterogeneity test: Q-value =18.95; P=0.96; I^2=0.0%), the combined OR was 1.85 (95% CI: 1.33–2.58; P<0.01). To examine the stability of the pooled OR, we performed a sensitivity analysis by sequentially removing individual studies. The results indicated that no single trial remarkably altered the pooled OR (Figure S2). Also, we performed a cumulative meta-analysis according to the publication years of the included trials. A consistent, statistically significant risk of TRDs was achieved in 2010 (OR: 2.30; 95% CI: 1.13–4.67; P=0.02) after only seven trials involving 3,545 patients had been included. Subsequently, 25 trials that enrolled an additional 8,768 patients until 2014

Table 1 Baseline characteristics of included randomized controlled trials in the meta-analysis

Cancer type	Reference	Trial phase	Treatment arms	Median age/years	Median TX (duration/ months[a])	Median PFS (months[a])	Median OS (months[a])	N of patients for analysis	N of deaths due to study drug	Jadad score
NSCLC	Paz-Ares et al[21]	III	Sorafenib 400 mg BID + GP	60	4.0	6.0	12.4	385	5	5
			Placebo + GP	58	4.2	5.5	12.5	384	2	
	Scagliotti et al[34]	III	Sorafenib 400 mg BID + TC	62	3.9	4.6	10.7	436	13	4
			Placebo + TC	63	4.2	5.4	10.6	459	4	
	Scagliotti et al[35]	III	Sunitinib 37.5 mg/day + erlotinib	61	4.3	3.6	9.0	473	4	5
			Placebo + erlotinib	61	4.3	2.0	8.5	477	4	
	Groen et al[30]	II	Sunitinib 37.5 mg/day + erlotinib	59	2.0	2.8	8.2	64	1	5
			Placebo + erlotinib	61	2.8	2.0	7.6	64	0	
	Heist et al[31]	II	Sunitinib 37.5 mg/day + PMX	NR	NR	3.7	6.7	41	2	2
			Sunitinib 37.5 mg/day	NR	NR	3.3	8.0	47	1	
			PMX	NR	NR	4.9	10.5	42	0	
	Heymach et al[32]	II	Vandetanib 100 mg/day + DTX	61	NR	4.4	13.1	42	0	2
			Vandetanib 300 mg/day + DTX	60	NR	2.8	7.9	44	0	
			Placebo + DTX	58	NR	4.0	13.4	41	0	
	Ahn et al[29]	II	Vandetanib 300 mg/day	61	2.0	2.7	15.6	75	0	2
			Placebo	60.5	1.8	1.7	20.8	42	0	
	Heymach et al[33]	II	Vandetanib 300 mg/day + TC	60	NR	5.6	10.2*	56	2	2
			Placebo + TC	59	NR	5.4	12.6*	52	0	
			Vandetanib 300 mg/day	73	NR	2.7	10.2*	73	0	
CRC	Tabernero et al[12]	II	Sorafenib 400 mg BID + mFOLFOX6	59.2	7.1	9.1	17.6	97	2	3
			Placebo + mFOLFOX6	60.3	7.9	8.7	18.1	101	1	
	Carrato et al[14]	III	Sunitinib 37.5 mg/day + FOLFIRI	59	NR	7.8	20.3	384	12	3
			Placebo + FOLFIRI	58	NR	8.4	19.8	379	4	
Breast cancer	Baselga et al[16]	II	Sorafenib 400 mg BID + Cap	55.1	7.9	6.4	22.9	112	0	5
			Placebo + Cap	54.4	5.3	4.1	20.9	112	2	
	Schwartzberg et al[39]	II	Sorafenib 400 mg BID + Gem/Cap	53.5	NR	3.4	13.4	79	1	3
			Placebo + Gem/Cap	54.2	NR	2.7	11.4	77	0	
	Gradishar et al[18]	II	Sorafenib 400 mg BID + PTX	50.6	6.4	6.9	16.8	115	2	5
			Placebo + PTX	53.1	6.8	5.6	17.4	118	0	
	Barrios et al[36]	III	Sunitinib 37.5 mg daily	53	2.2	2.8	15.3	238	5	3
			Cap	53	2.2	4.2	24.6	240	2	
	Bergh et al[22]	III	Sunitinib 37.5 mg/day + DTX	54	6.1	8.6	24.8	295	2	2
			Placebo + DTX	56	4.2	8.3	25.5	293	0	
	Johnston et al[38]	II	Pazopanib 400 mg/day + lapatinib	50	NR	NR	NR	76	0	2
			Lapatinib	54	NR	NR	NR	73	0	
	Boér et al[37]	II	Vandetanib 100 mg/day + DTX	54	4.8	8.2	NR	33	0	3
			Placebo + DTX	57	4.0	5.6	NR	29	1	

(*Continued*)

Table 1 (*Continued*)

Cancer type	Reference	Trial phase	Treatment arms	Median age/years	Median TX (duration/ months[a])	Median PFS (months[a])	Median OS (months[a])	N of patients for analysis	N of deaths due to study drug	Jadad score
	Rugo et al[24]	III	Axitinib 5 mg BID + DTX	55	NR	8.1*	NR	111	1	3
			Placebo + DTX	56	NR	7.1*	NR	56	0	
RCC	Escudier et al[5]	III	Sorafenib 400 mg BID	58	5.4	5.5	19.3	451	2	4
			Placebo	59	2.8	2.8	15.9	451	1	
	Hutson et al[20]	III	Sorafenib 400 mg BID	61	3.6	3.9	16.6	249	2	2
			Temsirolimus 25 mg/day	60	4.4	4.3	12.3	252	3	
	Motzer et al[40]	III	Sunitinib 50 mg for 4 weeks every 6 weeks	62	11.0	11.0	26.4	375	1	3
			Interferon	59	4.0	5.0	21.8	360	2	
	Sternberg et al[41]	III	Pazopanib 800 mg/day	59	7.4	9.2	Not reached	290	4	5
			Placebo	60	3.8	4.2	Not reached	145	0	
HCC	Cheng et al[42]	III	Sorafenib 400 mg BID	51	NR	2.8*	6.5	149	0	5
			Placebo	52	NR	1.4*	4.2	75	0	
	Kudo et al[43]	III	Sorafenib 400 mg BID	69	4.0	5.4*	29.7	229	0	3
			Placebo	70	4.7	3.1*	Not reached	227	0	
Pancreatic cancer	Gonçalves et al[17]	III	Sorafenib 400 mg BID + Gem	61	3.7	5.7	9.2	50	1	3
			Placebo + Gem	64	5.6	3.8	8.0	52	0	
	Reni et al[44]	II	Sunitinib 37.5 mg/day	61	3.0	3.2	10.6	28	0	2
			Observation	65	NR	2.0	9.2	27	0	
Prostate cancer	Horti et al[45]	II	Vandetanib 100 mg/day + DTX + prednisolone	67	4.2	NR	NR	43	0	3
			Placebo + DTX + prednisolone	67	8.4	NR	NR	43	2	
	Michaelson et al[11]	III	Sunitinib 37.5 mg/day + prednisone	69	3.3	5.6	13.1	581	12	3
			Placebo + prednisone	68	3.2	4.1	11.8	285	1	
Melanoma	Flaherty et al[13]	III	Sorafenib 400 mg BID + TC	61	NR	4.9	11.1	393	9	3
			Placebo + TC	59	NR	4.2	11.3	397	7	
	Hauschild et al[46]	III	Sorafenib 400 mg BID + TC	56	4.1	4.1	9.8	134	4	5
			Placebo + TC	55.1	4.0	4.2	9.8	134	0	
	McDermott et al[47]	II	Sorafenib 400 mg BID + dacarbazine	55	4.5	4.9	10.6	50	0	5
			Placebo + dacarbazine	60	2.8	2.7	12.0	51	0	
GIST	Demetri et al[23]	III	Sunitinib 50 mg for 4 weeks every 6 weeks	57	1.9	5.3	17.0	228	4	3
			Placebo	55	0.9	1.4	15.1	114	2	
	Demetri et al[25]	III	Regorafenib 160 mg/day	60	5.3	4.8	Not reached	132	2	5
			Placebo	61	1.6	0.9	Not reached	66	1	
Ovarian cancer	Herzog et al[19]	II	Sorafenib 400 mg BID	56.9	4.1	12.7	Not reached	123	0	3
			Placebo	54.4	12.1	15.7	Not reached	123	0	
PNET	Raymond et al[6]	III	Sunitinib 37.5 mg daily	56	4.6	11.4	Not reached	83	1	3
			Placebo	47	3.7	5.5	Not reached	82	1	
STS	van der Graaf et al[3]	III	Pazopanib 800 mg/day	56.7	3.8	4.6	11.9	239	1	5
			Placebo	51.9	1.9	1.6	10.4	123	0	

Thyroid cancer	Leboulleux et al[15]	II	Vandetanib 300 mg/day	63	6.4	11.1	Not reached	73	2	5	
			Placebo	64	5.9	5.9	Not reached	72	1		
	Elisei et al[4]	III	Cabozantinib 140 mg/day	55	6.8	11.2	NR	214	9	3	
			Placebo	55	3.5	4	NR	109	2		
SCLC	Arnold et al[48]	II	Vandetanib 300 mg/day	56.9	1.7	2.7	10.6	52	0	4	
			Placebo	62.4	2.8	2.8	11.9	53	0		
Urothelial cancer	Choueiri et al[49]	II	Vandetanib 100 mg/day + DTX	NR	1.4	2.6	5.9	70	1	5	
			Placebo + DTX	NR		1.6	7.0	72	0		
SCCHN	Limaye et al[50]	II	Vandetanib 100 mg/day + DTX	60	2.1	2.1	5.6	15	0	3	
			Placebo + DTX	56	1.4	0.7	6.3	14	2		

Notes: [a]When durations were reported as weeks, we converted them to months (1 week =7 days; 1 month =30 days). *Reported as time to progression.

Abbreviations: TX, treatment; PFS, progression-free survival; OS, overall survival; N, number; NSCLC, nonsmall-cell lung cancer; BID, twice daily; GP, gemcitabine + cisplatin; TC, paclitaxel + carboplatin; PMX, pemetrexed; NR, not reported; CRC, colorectal cancer; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; FOLFIRI, 5-fluorouracil, leucovorin, and irinotecan; Cap, capecitabine; Gem, gemcitabine; PTX, paclitaxel; DTX, docetaxel; RCC, renal cell cancer; HCC, hepatocellular cancer; GIST, gastrointestinal stromal cancer; PNET, pancreatic neuroendocrine cancer; STS, soft-tissue sarcoma; SCLC, small-cell lung cancer; SCCHN, squamous cell cancer of the head and neck.

had little or no effect on the OR, but it simply narrowed the 95% CI (Figure 3).

Subgroup analysis

Patients were further stratified according to tumor types. Significantly increased ORs of death with VEGFR-TKIs were found in patients with NSCLC (OR: 2.37; 95% CI: 1.19–4.73; *P*=0.01; incidence for VEGFR-TKIs arm versus control arm, 2.0% versus 0.8%) and CRC (OR: 2.84; 95% CI: 1.02–7.96; *P*=0.05; incidence for VEGFR-TKIs arm versus control arm, 2.9% versus 1.0%). The highest OR was noted in pancreatic cancer (OR: 3.18; 95% CI: 0.13–79.96; *P*=0.48), while the lowest OR was observed in patients with squamous cell carcinoma of the head and neck (OR: 0.16; 95% CI: 0.011–3.68; *P*=0.25). Despite the wide variation in ORs across different tumor types, there was no significant heterogeneity (*P*=0.89).

The risk of death among VEGFR-TKIs might be different. When we stratified patients by VEGFR-TKIs, a significantly increased risk of death was found with the use of sorafenib (OR: 1.99; 95% CI: 1.19–3.32; *P*=0.01) and sunitinib (OR: 2.12; 95% CI: 1.21–3.71; *P*=0.01). It was interesting to find that vandetanib nonsignificantly decreased the risk of TRD (OR: 0.72; 95% CI: 0.26–1.98; *P*=0.52). No significant heterogeneity was found when comparing the ORs of death with different VEGFR-TKIs (*P*=0.88).

To clarify the influence of drug combination on the ORs of death, a subgroup analysis was then conducted of the VEGFR-TKI schedule (VEGFR-TKIs alone or in combination with other agents). The pooled OR of death related to VEGFR-TKI monotherapy was 1.51 (95% CI, 0.82–2.78; *P*=0.18), while the OR of TRDs in combination therapy was 1.99 (95% CI, 1.33–2.97; *P*<0.01). The combining agents were further stratified. The results showed that VEGFR-TKIs in combination with chemotherapy significantly increased the risk of TRDs (OR: 1.92; 95% CI: 1.24–2.99; *P*<0.001), while VEGFR-TKIs plus target therapy did not reach significance (OR: 1.23; 95% CI: 0.35–4.31; *P*=0.74) (Table 2). In trials with VEGFR-TKI monotherapy, after excluding those with an active control,[20,36,40] we yielded similar results (OR: 1.65; 95% CI: 0.75–3.63; *P*=0.21).

We then explored the risk of death according to controlled therapy. The combined results showed that the use of VEGFR-TKIs was associated with a significantly increased risk of death when compared with nonplacebo therapy (OR: 1.88; 95% CI: 1.30–2.71; *P*<0.01), but not with placebo therapy (OR: 1.75; 95% CI: 0.81–3.79; *P*=0.15). However, the difference was considered not significant (*P*=0.82).

Table 2 Subgroup analysis for the incidence and OR associated with VEGFR-TKIs

Groups	Studies for incidence, n	TRDs, n/total, n/incidence, %		Studies for ORs, n	OR	95% CI	*P*-value	*P* (difference in ORs)
		VEGFR-TKIs	Control					
Overall	41	108/7,527/1.9	45/6,366/1.1	32	1.85	1.33–2.58	<0.01	0.96
VEGFR-TKIs								
Axitinib	1	1/111/0.9	0/56/0.9	1	1.53	0.06–38.26	0.79	0.88
Cabozantinib	2	12/302/4.0	2/151/1.7	1	2.35	0.50–11.07	0.28	
Pazopanib	3	5/605/1.0	0/341/0.5	2	3.06	0.37–25.58	0.30	
Regorafenib	1	2/132/1.5	1/66/1.5	1	1.00	0.09–11.23	1.00	
Sorafenib	15	41/3,052/1.8	20/3,013/1.0	11	1.99	1.19–3.32	0.01	
Sunitinib	10	42/2,749/1.9	16/2,321/0.9	10	2.12	1.21–3.71	0.01	
Vandetanib	9	5/576/1.6	6/481/3.1	6	0.72	0.26–1.98	0.52	
Tumor types								
Breast cancer	8	11/1,059/1.4	5/998/1.0	7	1.65	0.69–3.94	0.26	0.89
CRC	2	14/481/2.9	5/480/1.0	2	2.84	1.02–7.96	0.05	
GIST	2	6/360/1.7	3/180/1.7	2	1.00	0.25–4.05	1.00	
HCC	2	0/378/0.3	0/302/0.4	–	–	–	–	
Melanoma	3	13/577/2.4	7/582/1.5	2	1.83	0.75–4.51	0.19	
NSCLC	8	28/1,736/1.9	10/1,561/0.8	6	2.37	1.19–4.73	0.01	
Ovarian cancer	1	0/123/0.4	0/123/0.4	–	–	–	–	
Pancreatic cancer	2	1/78/1.9	0/79/1.3	1	3.18	0.13–79.96	0.48	
PNET	1	1/83/1.2	1/82/1.2	1	0.99	0.06–16.06	0.99	
Prostate cancer	2	12/624/2.0	3/328/1.9	2	1.30	0.05–37.39	0.88	
RCC	4	9/1,365/0.8	6/1,208/0.7	4	1.20	0.43–3.37	0.73	
SCCHN	1	0/15/3.1	2/14/14.3	1	0.16	0.01–3.68	0.25	
SCLC	1	0/52/0.9	0/53/0.9	–	–	–	–	
Soft-tissue sarcoma	1	1/239/0.4	0/123/0.4	1	1.55	0.06–38.42	0.79	
Thyroid cancer	2	11/287/3.9	3/181/1.7	2	2.25	0.61–8.30	0.22	
Urothelial cancer	1	1/70/1.4	0/72/0.7	1	3.13	0.13–78.13	0.49	
VEGFR-TKI regimens								
Monotherapy	17	33/3,228/1.6	15/1,561/0.9	11	1.51	0.82–2.78	0.18	0.44*
Combinations	22	70/4,082/2.0	30/3,711/1.3	19	1.99	1.33–2.97	<0.01	
Chemotherapy	18	53/2,888/2.2	25/2,812/1.4	16	1.92	1.24–3.00	<0.01	
Targeted therapy	3	5/613/0.9	4/614/0.8	2	1.23	0.35–4.31	0.74	
Endocrine therapy	1	12/581/2.1	1/285/0.4	1	5.99	0.78–46.29	0.09	
Trial phase								
Phase II	18	13/1,344/1.6	9/1,142/1.9	11	1.09	0.52–2.26	0.82	0.33
Phase III	23	95/6,183/2.0	36/5,224/0.9	21	2.11	1.45–3.07	<0.01	
Controlled therapy								
Placebo	13	25/2,338/1.7	8/1,682/0.9	8	1.75	0.81–3.79	0.15	0.82
Nonplacebo	28	83/5,189/2.0	37/4,684/1.2	24	1.88	1.30–2.71	<0.01	
Trial quality								
High	34	99/6,576/2.0	42/5,586/1.2	28	1.87	1.32–2.64	<0.01	0.81
Low	7	9/951/1.3	3/780/1.0	4	1.70	0.54–5.35	0.36	

Note: *Compared the difference between combination and single VEGFR-TKIs.

Abbreviations: OR, odds ratio; VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors; n, number; CI, confidence interval; CRC, colorectal cancer; GIST, gastrointestinal stromal cancer; HCC, hepatocellular cancer; NSCLC, nonsmall-cell lung cancer; PNET, pancreatic neuroendocrine cancer; RCC, renal cell cancer; SCCHN, squamous cell cancer of the head and neck; SCLC, small-cell lung cancer; TRDs, treatment-related deaths.

To determine whether the risk of death differed in different trial phases, a subgroup analysis of Phase II versus Phase III trials were performed. The ORs of death due to the study drug were 1.09 (95% CI: 0.52–2.26; P=0.82) and 2.11 (95% CI: 1.45–3.07; P<0.01) in Phase II and Phase III trials, respectively. No statistically significant difference was observed when comparing ORs in both phases (P=0.33). The results of the subgroup analysis are summarized in Table 2.

Publication bias

No evidence of a publication bias was detected for the OR by either Egger's test (P=0.46) or Begg's test (P=0.39).

Discussion

Angiogenesis is mainly mediated by the VEGF pathway, and this pathway plays an important role in tumor growth and metastasis.[1] Until now, several angiogenesis inhibitors that

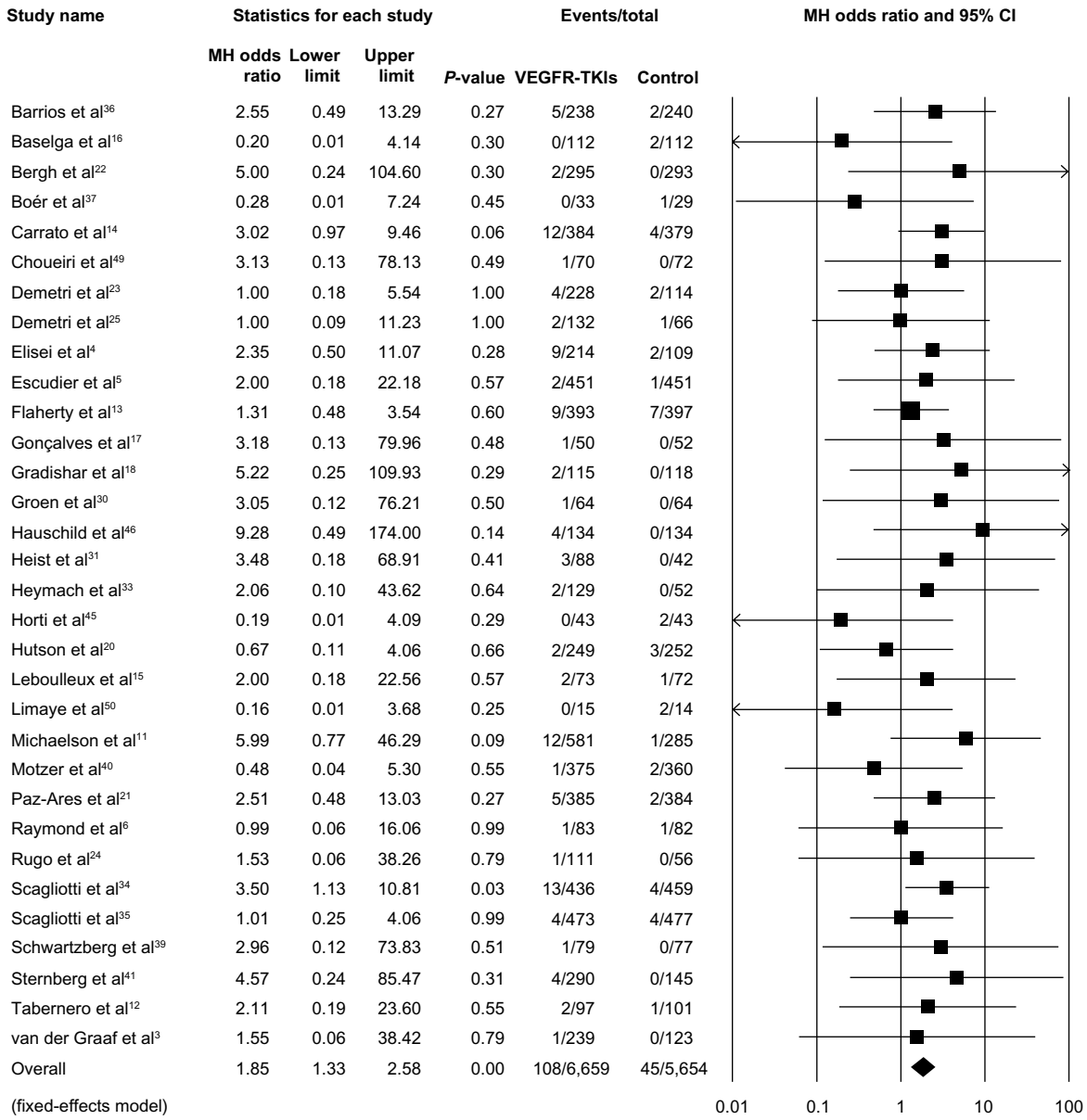

Figure 2 Odds ratio of death associated with VEGFR-TKIs by individual study.
Notes: Test for heterogeneity: Q=42.3, I^2=5.5%, P=0.37.
Abbreviations: MH, Mantel–Haenszel; CI, confidence interval; VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors.

target the VEGF pathway have moved from preclinical studies to well established clinical use. Although angiogenesis inhibitors present a favorable toxicity spectrum to traditional cytotoxic chemotherapy agents, their potential TRDs also raise concerns. Actually, previous meta-analyses have demonstrated an increased risk of FAEs using VEGFR-TKIs.[8,9] However, the interpretation of their results was hampered by either the ambiguous definition of TRDs or too small sample sizes. The actual risk of death related to VEGFR-TKIs deserves further evaluation. We therefore sought to investigate this issue with more up-to-date data and a detailed subgroup analysis. To our knowledge, this is currently the largest meta-analysis concerning the incidence and risk of death due to VEGFR-TKIs in patients with malignant tumors. The study demonstrates that VEGFR-TKIs could significantly increase the risk of TRDs when compared with non-VEGFR-TKI regimens.

This meta-analysis of 41 RCTs showed that the pooled incidence of VEGFR-TKI-related deaths was 1.9%, which was lower than the 2.26% incidence previously reported by Sivendran et al.[8] The explanation is that Sivendran et al's study included more FAEs. The authors included all events regardless of attribution to treatment protocol if only they are not related to cancer progression, which might have

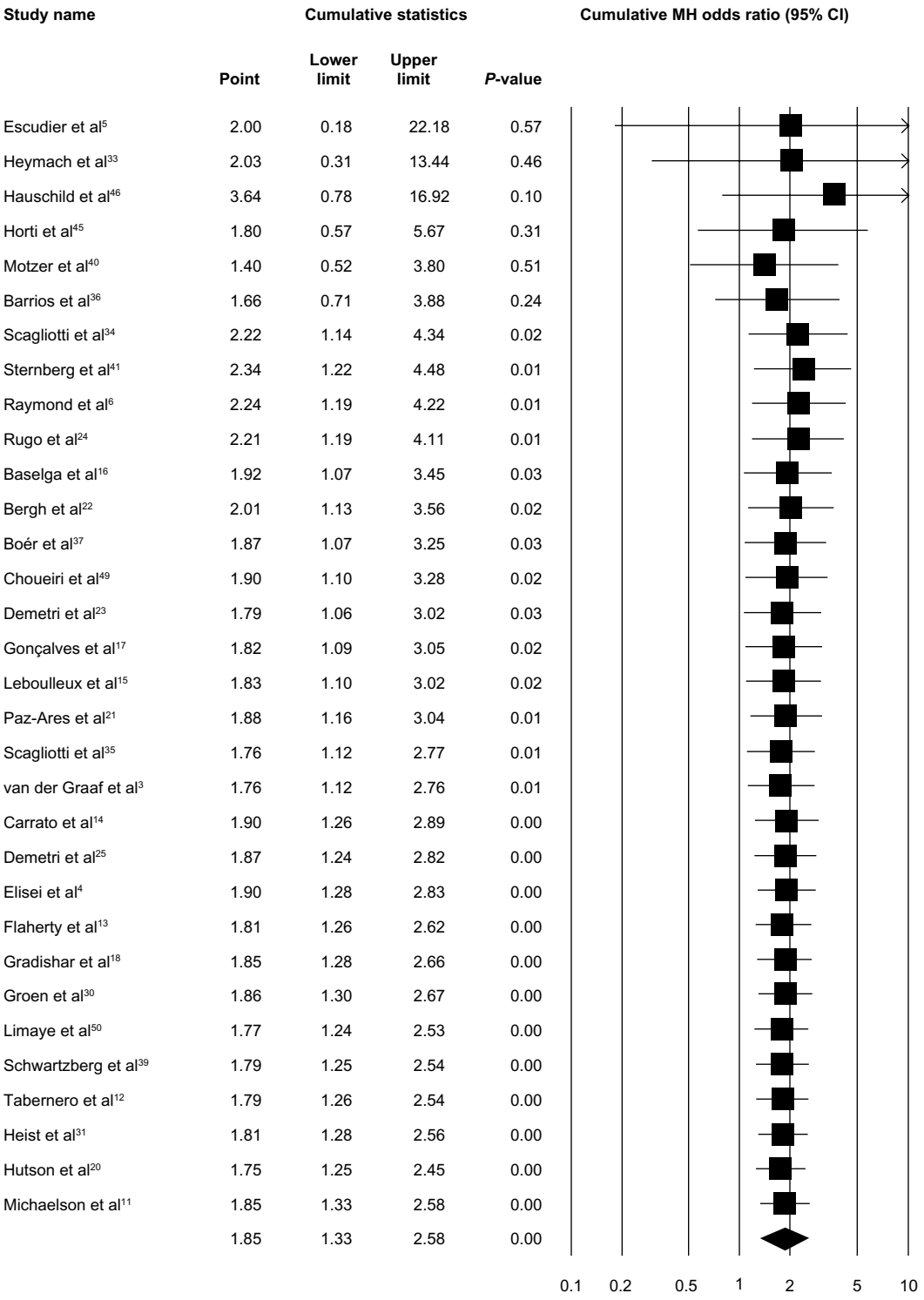

Figure 3 Forest plot of the odds ratio for death events with VEGFR-TKIs: cumulative analysis in the order of publication years.
Abbreviations: MH, Mantel–Haenszel; CI, confidence interval; VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors.

overestimated the overall incidence of TRDs. In another meta-analysis which adopts similar inclusion criteria with the present one, the summarized incidence was reported to be 1.5%.[9] Taken together, it could be concluded that about two out of 100 patients receiving VEGFR-TKIs die from these drugs. The present study also demonstrated that the use of VEGFR-TKIs could significantly increase the risk of TRDs when compared with controls (OR: 1.85; 95% CI: 1.33–2.58; $P<0.001$). Similar results were also observed in a previous study,[9] though the risk of TRDs was a little higher (relative

risk (RR): 2.23; 95% CI: 1.12–4.44; *P*=0.02). This could be attributed to the limited sample size of that study (only 4,679 patients from ten RCTs were included). In our cumulative meta-analysis by publication year, almost the same results with that study[9] were found when ten RCTs were incorporated into the analysis (OR: 2.21; 95% CI: 1.19–4.11; *P*=0.01), yet the present study was able to include even more RCTs and it yielded more robust results (with a narrower 95% CI).

Upon the exploratory subgroup analysis, a significantly increased risk of death due to VEGFR-TKIs was found in patients with NSCLC and CRC. A wide variation of ORs across different cancer types could suggest that there may be a tumor-specific interaction between VEGFR-TKIs and tumor type in terms of toxicity. The results indicate that attention should be paid to the risk of death using VEGFR-TKIs in NSCLC or CRC patients. As for different kinds of VEGFR-TKIs, sorafenib and sunitinib were found to significantly increase the risk of death when compared with the control arms. Due to the wide clinical use of sorafenib and sunitinib in treating malignant tumors, it is important to inform patients of the potential FAEs of these two drugs. The results of the subgroup analysis were similar to the results from Zhang et al's study,[51] which specifically investigated the risk of treatment-related mortality with sorafenib. Additionally, in the present study it was noted that the use of vandetanib non-significantly decreased the risk of TRDs. Interestingly, though VEGFR-TKIs are known to cause hemorrhage, a previous meta-analysis also reported that vandetanib nonsignificantly decreased the risk of bleeding.[52] While some non-overlapping targets of vandetanib, when compared with other VEGFR-TKIs, may result in different side effects, the data are insufficient to explain such differences. Molecular and clinical studies focusing on this issue are needed. We also found that only VEGFR-TKIs in combination with other antineoplastic agents had a significantly increased OR (OR: 1.99; 95% CI: 1.33–2.97; *P*<0.01), while VEGFR-TKI monotherapy did not yield a significant OR (OR: 1.51; 95% CI: 0.82–2.78; *P*=0.18). This result is different from those from the study by Sivendran et al,[8] which compared VEGFR-TKI monotherapy with controls. The authors found a significantly increased risk of FAEs with VEGFR-TKI monotherapy (RR: 1.64; 95% CI: 1.16–2.32; *P*=0.01). There are several possible explanations for this inconsistency: 1) as stated above, all FAEs were included in Sivendran et al's study,[8] which might have overestimated the death risk associated with VEGFR-TKIs; and 2) there was a difference in the sample size and the distribution of cancer types – the present study included more trials, and the major cancer type was breast cancer, while the major type of cancer in Sivendran et al's study[8] was renal cell cancer. Nevertheless, the risk of death associated with VEGFR-TKI monotherapy should not be ignored because the lower limit of its 95% CI is close to 1. A more recent study found that the addition of VEGFR-TKIs to cytotoxic chemotherapy significantly increased the risk of FAEs.[53] This also supports the subgroup analysis of the present meta-analysis, though the authors of that study have also focused on FAEs but not TRDs. Further studies are needed to explore the underlying drug–drug interactions and to determine the impacts of adding other agents to VEGFR-TKIs.

The causes of TRDs with VEGFR-TKIs were also examined. The most common causes included cardiopulmonary insufficiency (11.1%) and thromboembolism (8.3%), which were in accordance with the VEGFR-TKI toxicity spectrum, as previously reported.[54,55] Actually, the VEGF pathway is also involved in normal physiological processes such as the maintenance of vascular endothelial function and myocardiocyte well-being. Blocking the VEGF pathway may disrupt the integrity of micro- and macrovessels and impact the growth of myocardiocytes, which may lead to thromboembolic events and cardiac failure.[7] Other common causes of TRDs with VEGFR-TKIs include hemorrhage, cerebrovascular accidents, neutropenia, and gastrointestinal disorders. It is therefore important to monitor and identify these serious AEs in patients treated with VEGFR-TKIs so that timely interventions can be applied to mitigate risk.

Meta-analysis is a useful tool for analyzing rare events like mortality because it can comprehensively synthesize data from different studies to achieve a more robust estimate of effects. However, several limitations need to be considered in the present meta-analysis. Firstly, this meta-analysis was based on study-level evidence. Therefore, confounding factors like patients' comorbidities, prior chemotherapeutic exposure, demographic characteristics, and concomitant treatment could not be incorporated into the analysis. Also, a time-to-event analysis for TRDs could not be conducted, precluding the calculation of hazard ratios. In spite of this, a review by Bennett et al[56] showed that the results between patient- and study-level meta-analyses were remarkably similar, suggesting that study-level meta-analysis could also provide sufficient power. Secondly, the attribution of death events to the treatment protocol was judged by investigators, which lacked objective criteria. Hence, the exact cause of death could not be fully explored even in patient-level studies. Nevertheless, by using meta-analysis to generate the combined results, such bias could be reduced as much as possible. Thirdly, all of the included studies were carried out

with patients who had sufficient organ function at enrollment. Most of the trials excluded patients with brain metastasis, history of or active hemorrhage, and uncontrolled hypertension. Therefore, the overall incidence of TRDs reported here might be lower when compared with those at the population level. However, the inclusion and exclusion criteria adopted for the experiment and control groups were the same. This should lead to equal underreporting of TRDs in both arms, and have subsequently less impact on the overall risk of death due to VEGFR-TKIs.

Conclusion

In summary, the present work pointed out a significantly increased risk of death due to VEGFR-TKI regimens. VEGFR-TKIs, in combination with other antineoplastic agents but not VEGFR-TKI monotherapy, significantly increased the risk of TRDs. It is important to carefully assess the risk–benefit for individual patients and to take into account the risk factors associated with the patients. Correlative studies to identify the predictive markers for treatment efficacy and toxicity are also warranted. Studies of genetic susceptibility loci for VEGFR-TKI-associated deaths are highly recommended. Improved the reporting of TRDs in clinical trials should be mandated to better define the excess risk of TRDs associated with new and existing therapies.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

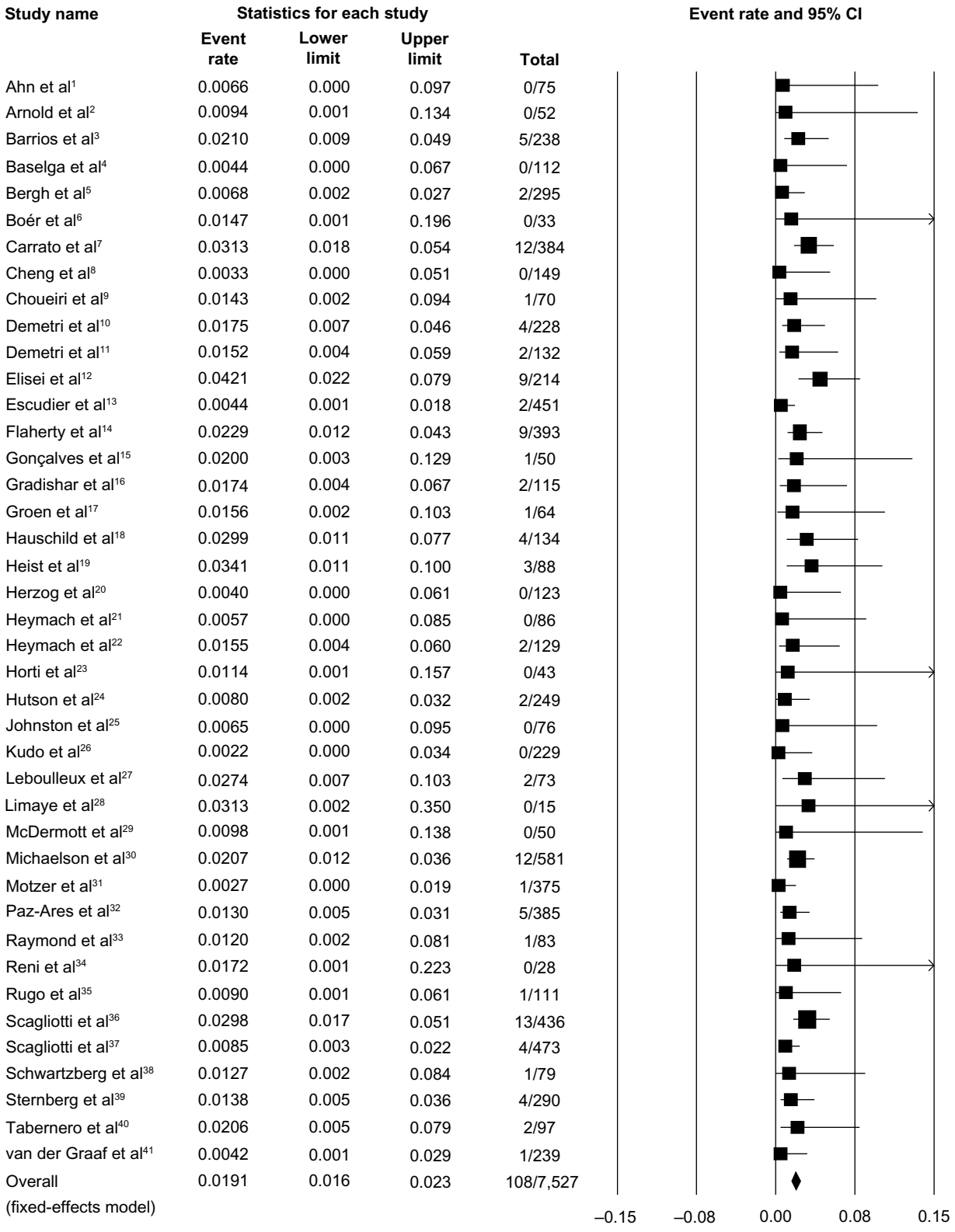

Figure S1 Incidence of treatment-related deaths with VEGFR-TKIs by individual study.
Note: Test for heterogeneity: Q=42.3, I^2=5.5%, P=0.37.
Abbreviations: CI, confidence interval; VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors.

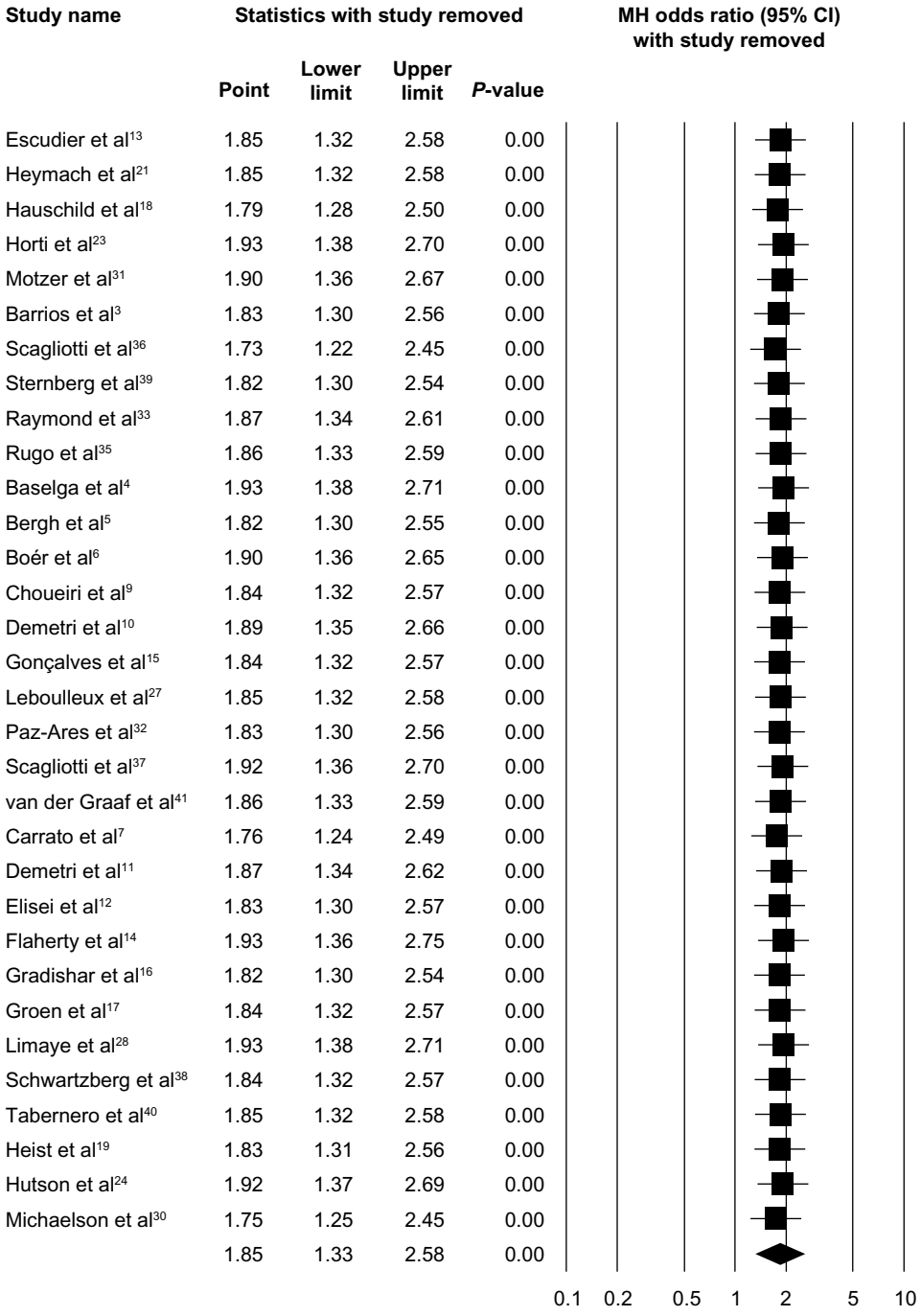

Figure S2 Forest plot of the odds ratio for death events with VEGFR-TKIs: sensitivity analysis by sequentially omitting individual studies.
Abbreviations: MH, Mantel-Haenszel; CI, confidence interval; VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors.

Table S1 Categorized causes of deaths due to VEGFR-TKIs

Causes	VEGFR-TKIs (%)	Control (%)
Hemorrhage	5 (4.6)	4 (8.9)
Cerebrovascular accident	5 (4.6)	2 (4.4)
Renal failure	1 (0.9)	0 (0)
Neutropenia	5 (4.6)	0 (0)
Thromboembolism	9 (8.3)	3 (6.7)
Pulmonary disorders	4 (3.7)	6 (13.3)
Sudden death	3 (2.8)	0 (0)
Sepsis	5 (4.6)	2 (4.4)
Cardiopulmonary insufficiency	12 (11.1)	5 (11.1)
Hepatic failure	5 (4.6)	1 (2.2)
Gastrointestinal diseases	7 (6.5)	0 (0)
Other	4 (3.7)	6 (13.3)
Unknown	43 (39.8)	16 (35.6)
Total	108 (100)	45 (100)

Abbreviation: VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors.

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