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Congestive heart failure risk in cancer patients treated with vascular endothelial growth factor tyrosine kinase inhibitors: a systematic review and meta-analysis of 36 clinical trials

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AIMS

Congestive heart failure (CHF) associated with vascular endothelial growth factor tyrosine-kinase inhibitors (VEGFR-TKIs) has emerged as a relevant problem in clinical and scientific communities. We performed an up-to-date, comprehensive meta-analysis to determine the overall incidence and risk of CHF in cancer patients receiving VEGFR-TKIs.

METHODS

The databases of PubMed, Web of Science and abstracts presented at the American Society of Clinical Oncology up to August 31 2013 were searched for relevant articles. Statistical analyses were conducted to calculate the summary incidence, odds ratio (OR) and 95% confidence intervals (CIs) by using either random effects or fixed effect models according to the heterogeneity of included studies.

RESULTS

A total of 10 553 patients from 36 clinical trials were included. The overall incidence of all grade and high grade CHF associated with VEGFR-TKIs was 3.2% (95% CI 1.8%, 5.8%) and 1.4% (95% CI 0.9%, 2.3%), respectively. The use of VEGFR-TKIs significantly increased the risk of developing all grade (OR 2.37, 95% CI 1.76, 3.20, $P < 0.001$) and high grade (OR 3.51, 95% CI 1.74, 7.05, $P < 0.001$) CHF. In subgroup analyses, the risk of CHF did not significantly vary with tumour types ($P = 0.071$ for all grade; $P = 0.72$ for high grade) and VEGFR-TKIs ($P = 0.55$ for all grade; $P = 0.99$ for high grade). Meta-regression indicated that CHF might possibly occur early in the treatment of VEGFR-TKIs. No evidence of publication bias was observed.

CONCLUSION

The use of VEGFR-TKIs is associated with a significantly increased risk of developing congestive heart failure in cancer patients. Clinicians should be aware of this risk and provide close monitoring in patients receiving these therapies.

Introduction

In recent years, anti-angiogenesis targeted therapies have proven to be a promising therapeutic strategy in patients with cancer [1, 2]. Several newly-developed agents that target the vascular endothelial growth factor (VEGF) signalling pathway, such as the small molecular VEGF receptor inhibitors (e.g. sunitinib, sorafenib, vandetanib, pazopanib, axitinib, cediranib, tivozanib, regorafenib, cabozantinib, brivanib and ramucirumab) and the

anti-VEGF monoclonal antibody bevacizumab, have shown encouraging treatment benefits in patients with various types of solid tumours [3–16]. However, as the VEGF pathway is not only essential for normal growth and development, but also critical to physiological response and homeostasis in many organs and functions in adulthood [17], a variety of adverse effects are anticipated with pharmacological blockage of this pathway. Indeed, the clinical adverse event profiles are extensive [18–20]. The adverse effects attributed to VEGF inhibition include hypertension, arterial thromboembolic events (ATEs), proteinuria or renal dysfunction, wound complications, haemorrhage and gastrointestinal perforation, which have been systematically defined in previous studies [21–36].

Congestive heart failure (CHF) is a rare but serious adverse event associated with VEGF-targeted agents. A previous meta-analysis demonstrated that the use of bevacizumab significantly increased the risk of CHF when compared with controls (relative risk (RR) 4.74, 95% CI 1.66, 11.18, $P = 0.001$) [37]. The VEGFR-TKI agent sunitinib has been also associated with an increased risk of CHF in one meta-analysis [38]. However, that report has several limitations. Although the meta-analysis included 16 clinical trials, most of these were single arm trials, and only four randomized controlled trials (RCTs) were included in the meta-analysis and thus the power to investigate the risk of CHF with sunitinib was small and the combined results might have been affected by a single large RCT. In addition, several newly developed VEGFR-TKIs which share a similar spectrum of target receptors with sunitinib might be also associated with increased risk of developing CHF. Indeed, CHF related to these drugs has been sporadically reported in recent clinical trials [7, 39–43]. However the contributions of these newly developed VEGFR-TKIs to CHF are still unknown. As a result, we conducted this meta-analysis of all available clinical trials to determine the overall incidence and risk of CHF associated with VEGFR-TKIs.

Methods

Data sources

We conducted an independent review of citations from PubMed between January 1 1966 and August 31 2013. Keywords were sorafenib, nexavar, BAY43-9006, sunitinib, sutent, SU11248, pazopanib, votrient, GW786034, vandetanib, caprelsa, ZD6474, axitinib, cediranib, tivozanib, regorafenib, cabozantinib, brivanib, ramucirumab, clinical trials and cancer. The search was limited to prospective clinical trials published in English. The search strategy also used text terms such as angiogenesis inhibitors and vascular endothelial growth factor receptor-tyrosine kinase inhibitors to identify relevant information. We also performed independent searches using Web of Science databases between January 1 1966 and August 31 2013, to ensure that no clinical trials were overlooked. Additionally, we searched the clinical trial registration website (http://www.ClinicalTrials.gov) to obtain information on the registered prospective trials. We also searched abstracts and virtual meeting presentations from the American Society of Clinical Oncology (http://www.asco.org/ASCO) conferences that took place between January 2004 and January 2013. Reference lists from relevant primary studies and review articles were also examined to find additional publications. Each publication was reviewed and in cases of duplicate publication only the most complete, recent and updated report of the clinical trial was included in the meta-analysis.

Study selection was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [44]. Clinical trials that met the following criteria were included: (1) prospective phase II and III trials, expanded access protocols (EAPs), (2) participants assigned to treatment with VEGFR-TKIs (alone or in combination at any dosage or frequency) and (3) available data regarding events or incidence of CHF and sample size. Phase I trials were excluded because of inter-study variability in drug dosing as well as the small number of patients in these trials.

Data extraction

Data abstraction was conducted independently by two investigators (WXQ and ZS), and any discrepancy between the reviewers was resolved by consensus. For each study, the following information was extracted: first author's name, year of publication, trial phase, number of enrolled subjects, treatment arms, number of patients in treatment and controlled groups, underlying malignancy, median age, median treatment duration, median progression-free survival, number of CHF events, name and dosage of the VEGFR-TKIs agents. We considered the reporting of left ventricular ejection fraction (LVEF) decline or dysfunction and CHF not otherwise specified as CHF-related adverse events. Adverse events of all and high grade (≥ grade 3), as recorded according to the National Cancer Institute's common terminology criteria for adverse events (version 2 or 3), were extracted for analysis [45]. The quantitative five point Jadad scale was used to assess the quality of the included RCTs based on the reporting of the studies' methods and results [46].

Statistical analysis

The principal summary measures were incidence, odds ratio (OR) and corresponding 95% confidence intervals (CIs). For the calculation of incidence, the number of patients experiencing CHF and total number of patients treated with VEGFR-TKIs were extracted from the safety profiles of all selected clinical trials; the proportion of patients with CHF and 95% CI were derived for each study. We used the Peto method to calculate the ORs

and 95% CIs because this method provided the best CI coverage and was more powerful and relatively less biased than the fixed or random effects analysis when dealing with low event rates [47]. Between study heterogeneity was estimated using the χ^2-based Q statistic [48]. Heterogeneity was considered statistically significant when $P_{heterogeneity} < 0.1$. If heterogeneity existed, data were analyzed using a random effects model. In the absence of heterogeneity, a fixed effects model was used. A statistical test with a P value less than 0.05 was considered significant. To assess the stability of the results, sensitivity analysis was carried out by sequential omission of individual studies. Additionally, to test whether effect sizes were moderated by differences in the length of treatment, we had carried out meta-regressions with differences in the median length of experimental treatments (expressed in months) as a predictor and the odds ratio as a dependent variable. The presence of publication bias was evaluated by using the Egger tests. 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).

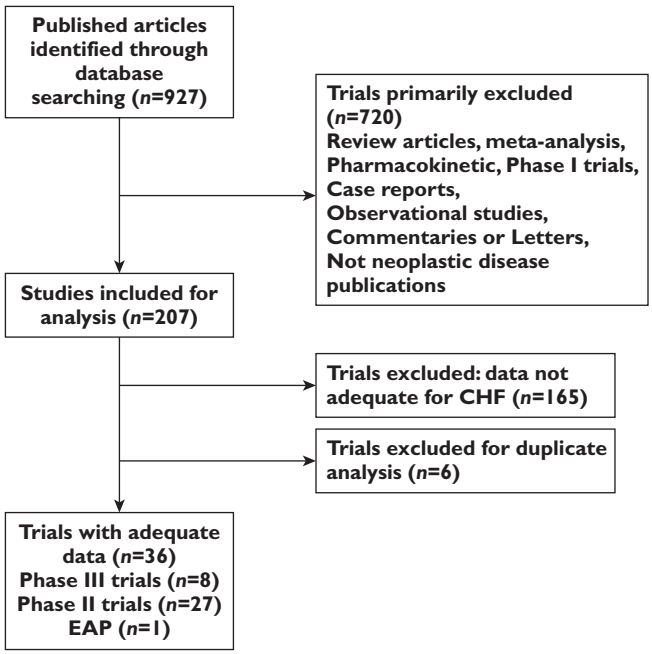


Figure 1

Selection process for prospective clinical trials included in the meta-analysis

Results

Search results

Our search yielded 927 clinical studies relevant to VEGFR-TKIs (sunitinib, sorafenib, pazopanib, vandetanib, axitinib, cediranib, tivozanib, regorafenib, cabozantinib, brivanib and ramucirumab). After excluding review articles, phase I studies, case reports, meta-analyses and observation studies (Figure 1), we selected 36 clinical trials, including eight phase III, 27 phase II trials and one extended access programme (EAP) trial, for the purposes of analysis (Table 2). A total of 10 553 patients from 36 clinical trials were included for analysis. The characteristics of patients and studies are listed in Table 1. According to the inclusion criteria of each trial, patients were required to have adequate hepatic, renal and haematological function. Underlying malignancies included renal cell cancer [14, 15, 40, 49–57] (12 trials), breast cancer [58–63] (six trials), sarcoma [7, 39, 64, 65] (four trials), thyroid cancer [42, 66, 67] (three trials), gastro-intestinal stromal tumour (GIST) [13, 68] (two trials), primitive neuroectodermal tumour (PNET) [69] (one trial), hepatocellular carcinoma [70] (one trial), pancreatic cancer [43] (one trial), cervical cancer [71] (one trial), colorectal cancer (one trial) [16], gastric cancer [41] (one trial), prostate cancer [72] (one trial), non-small cell lung cancer (NSCLC) [73] (one trial) and advanced neuroendocrine tumours [74] (one trial). The most commonly reported adverse event meeting our criteria was LVEF decline (16 studies), with congestive failure in 12 studies and LV dysfunction in eight studies. The quality of 15 included RCTs was high. Ten trials had Jadad scores of 5 and four trials did not mention the blinding of allocation clearly in the randomization process and thus had Jadad scores of 3. Another one trial had a Jadad score of 2.

Incidence of CHF

A total of 6903 patients from 27 treatment arms who received VEGFR-TKIs as a single agent were available for all grade CHF analysis. There were 174 total CHF events among these patients. The incidence of all grade CHF ranged between 0% and 11.5%. Using a random effect model (χ^2-based Q statistic test: Q = 269.35, $P < 0.001$, I^2 = 90%), the overall incidence of all grade CHF was 3.2% (95% CI 1.8, 5.8%, Figure 2). High grade CHF was associated with increased morbidity and could result in dose modification or treatment interruption. A total of 6896 patients prescribed VEGFR-TKIs as a single agent from 26 treatment arms were included for analysis. The incidence of high grade CHF ranged from 0% to 4.8%. The summary incidence of high grade CHF was 1.4% (95% CI 0.9, 2.3%, Figure 2) according to the random effects model. We also performed a sub-group analysis to investigate the incidence difference according to tumour types, VEGFR-TKIs and phase of trials. Our results demonstrated that the incidence of CHF did not significantly vary with tumour types and phase of trials (Table 2). The incidence of all grade CHF associated pazopanib (6.1%) and cediranib (5.9%) was higher than that of vandetanib (0.4%) and ramucirumab

Table 1

Baseline characteristics of the 36 trials included in the meta-analysis ($n = 10\,553$)

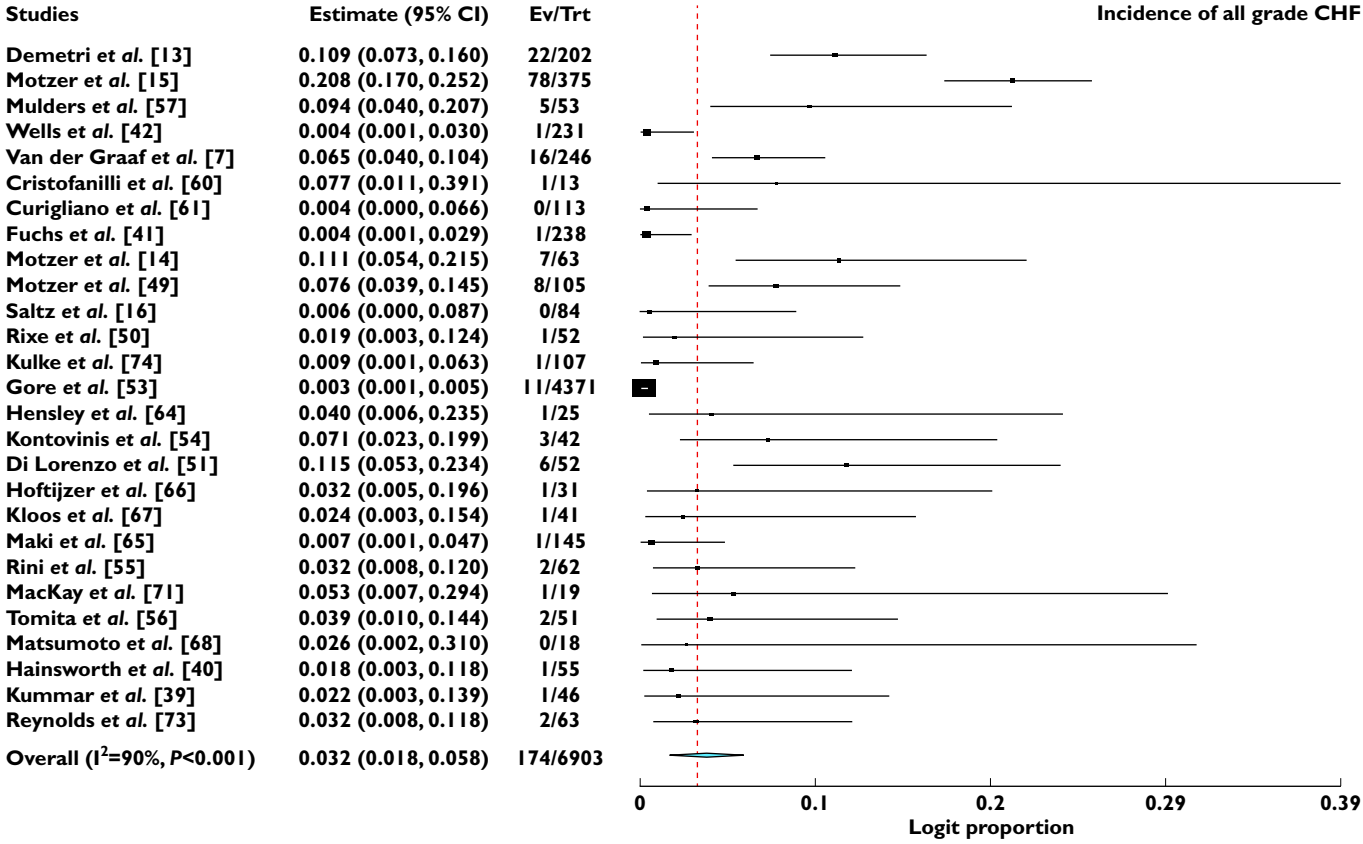
Authors/phase	Histology	Patients enrolled	Treatment arm	Number for analysis	Median age (years)	Median treatment duration (months)	Median PFS/TTP (months)	Median OS (months)	Number of high grade CHF	Reported events	Jadad score
Demetri *et al.* [13]/III*	GIST	312	Sunitinib 50 mg d1^{-1}-28, q6w	202	58	1.9	6	NR	3	LVEF decline	5
			Placebo	102	55	1	1.5	NR	0		
Motzer *et al.* [15]/III*	RCC	750	Sunitinib 50 mg d1^{-1}-28, q6w	375	62	6	11	NR	13	LVEF decline	3
			INF 9 MUI 3 times weekly	360	59	4	2	NR	4†		
Barrios *et al.* [58]/III*	HER-2 negative BC	482	Sunitinib 37.5 mg qd + capecitabine 1 250 mg m^{-2} d1–14 bid po, q3w.§	238	53	2	2.8	15.3	1	Congestive failure	3
			Capecitabine 1 250 mg m^{-2} d1–14 bid po, q3w	244	53	2	4.2	24.6	0		
Abou-Alfa *et al.* [70]/II*	HCC	96	Doxorubicin + sorafenib 400 mg bid po qd	47	66	4	6	13.7	1	LV dysfunction	5
			Doxorubicin + placebo	49	65	1.9	2.7	6.5	0		
Raymond *et al.* [69]/III*	PNET	171	Sunitinib 37.5 mg qd po	86	56	4.6	11.4	NR	2	Cardiac failure	5
			placebo	85	47	3.7	5.5	NR	0		
Kindler *et al.* [43]/II*	Pancreatic carcinoma	632	Axitinib 5 mg bid po + gemcitabine 1000 mg m^{-2} d 1, 8, 15 q4w.	314	61	2.8	4.4	8.5	1	Cardiac failure	5
			Placebo + gemcitabine 1000 mg m^{-2} d1, 8, 15. q4w.	316	62	2.3	4.4	8.3	0		
Bergh *et al.* [59]/III*	MBC	593	Sunitinib 37.5 mg qd po q3w. + docetaxel	296	54	6.1	8.6	24.8	1	Cardiac failure	5
			Placebo + ocetaxel	297	56	4.2	8.3	25.5	0		
Mulders *et al.* [57]/II*	RCC	71	Cediranib 45 mg qd po	53	60	12	12.1	NR	1	LVEF decline	5
			placebo	18	61	NR	2.8	NR	0		
Wells *et al.* [42]/III*	Thyroid cancer	331	Vandetanib 300 mg qd po	231	50.7	21	30.5	NR	1	Cardiac failure	5
			placebo	100	53.4	9.3	19.3	NR	0		
van der Graaf *et al.* [7]/III*	STS	372	Pazopanib 800 mg qd po	246	51.9	3.83	4.6	12.5	3	LVEF decline	5
			placebo	123	56.7	1.89	1.6	10.7	0		
Cristofanilli *et al.* [60]/II*	Inflammatory BC	163	Pazopanib 800 mg qd po + lapatinib 1500 mg	38	52	2.8	NR	16.2	0	LVEF decline	3
			Placebo + apatinib 1500 mg	38	52	3.8	NR	14.7	0		
			Placebo + apatinib 1500 mg	36	53	3.76	NR	15.9	0		
			pazopanib 400 mg qd po + lapatinib 1000 mg	38	54	2.96	NR	NR	0		
			pazopanib 800 mg qd po	13	55	1.73	NR	NR	0		
Curigliano *et al.* [61]/II*	Triple-negative BC	217	Sunitinib 37.5 mg qd po q3w.	113	52	NR	2	9.4	0	Cardiac failure	2
			standard of care	104	52	NR	2.7	10.5	1		
Fuchs *et al.* [41]/III*	Gastric or gastro-oesophageal junction cancer	355	Ramucirumab 8 mg kg^{-1} q2w.	238	60	1.87	2.1	5.2	0	Cardiac failure	5
			placebo	117	60	1.4	1.3	3.8	0		
Hyams *et al.* [62]/II*	MBC	62	Cediranib 45 mg qd po + fulvestrant 500 mg q4w.	31	NR	NR	7.4	NR	0	LVEF decline	5
			Placebo + ulvestrant 500 mg q4w.	31	NR	NR	3.7	NR	0		

Table 1

Continued

Authors/phase	Histology	Patients enrolled	Treatment arm	Number for analysis	Median age (years)	Median treatment duration (months)	Median PFS/TTP (months)	Median OS (months)	Number of high grade CHF	Reported events	Jadad score
Johnston *et al.* [63]/II*	HER-2 positive BC	177	Pazopanib 400 mg qd po + lapatinib 1000 mg	69	50	NR	NR	NR	0	LV dysfunction	3
			Placebo + lapatinib 1500 mg	72	54	NR	NR	NR	0		
			Lapatinib + pazopanib 800 mg qd po	36	54	NR	NR	NR	0		
Motzer *et al.* [14]/II	RCC	63	Sunitinib 50 mg d1^{-1}-28 q6w	63	60	9	8.7	NR	1	LVEF decline	NA
Motzer *et al.* [49]/II	RCC	106	Sunitinib 50 mg d1^{-1}-28 q6w	105	56	7.5	8.3	NR	5	LVEF decline	NA
Saltz *et al.* [16]/II	CRC	84	Sunitinib 50 mg d1^{-1}-28 q6w, bevacizumab native	40	56.5	NR	2.3	NR	0	LVEF decline	NA
			Sunitinib 50 mg d1^{-1}-28 q6w, pretreated with bevacizumab	42	57.5	NR	2.8	NR	0		
Rixe *et al.* [50]/II	RCC	52	Axitinib 5 mg bid po qd	52	59	9.4	15.7	29.9	1	LVEF decline	NA
Kulke *et al.* [74]/II	pancreatic carcinoid	107	Sunitinib 50 mg d1^{-1}-28 q6w	107	56	12.5	7.7	16.4	1	CHF	NA
Dror Michaelson *et al.* [72]/II	prostate cancer	34	Sunitinib 50 mg d1^{-1}-28 q6w	34	71	1.5	NR	NR	1	LV dysfunction	NA
Escudier *et al.* [9]/II	RCC	107	Sunitinib 37.5 qd po	105	59	8.4	8.2	19.8	1	LVEF decline	NA
Gore *et al.* [53]/II	RCC	4564	Sunitinib 50 mg d1^{-1}-28 q6w	4371	59	7.5	10.9	18.4	10	CHF	NA
Hensley *et al.* [64]/II	Uterine leiomyosarcoma	25	Sunitinib 50 mg d1^{-1}-28 q6w	23	56	NR	1.54	15.1	0	LVEF decline	NA
Kontovinis *et al.* [54]/II	RCC	42	Sunitinib 50 mg d1^{-1}-28 q6w	42	64	NR	8.9	16.23	1	LVEF decline	NA
Di Lorenzo *et al.* [51]/II	RCC	52	Sorafenib 400 mg qd po q8w.	52	60	4.1	3.73	7.5	1	LV dysfunction	NA
Hoftijzer *et al.* [66]/II	Thyroid carcinoma	31	Sorafenib 400 mg qd po q8w.	31	65	NR	13.5	NR	NR	CHF	NA
Kloos *et al.* [67]/II	Thyroid carcinoma	41	Sorafenib 400 mg qd po q8w. Previously treated	19	67	8.73	16	23	1	LV dysfunction	NA
			Sorafenib 400 mg qd po q8w. Native	22	56	9.87	10	37.5	0		
Maki *et al.* [65]/II	Sarcoma	147	Sorafenib 400 mg qd po q4w.	145	55	NR	3.2	14.3	1	Cardiac ejection fraction	NA
Rini *et al.* [6]/II	RCC	62	Axitinib 5 mg bid po qd	62	60	6.2	7.4	13.6	NR	CHF	NA
MacKay *et al.* [71]/II	Cervical cancer	19	Sunitinib 50 mg d1^{-1}-28 q6w	19	44	NR	3.5	NR	0	LV dysfunction	NA
Tomita *et al.* [56]/II	RCC	51	Sunitinib 50 mg d1^{-1}-28 q6w	51	56.6	4.9	12.2	33.1	1	LVEF decline	NA
					61.1	6.5	10.6	32.5			
Matsumoto *et al.* [68]/II	GIST	18	Sunitinib 50 mg d1^{-1}-28 q6w	18	58.7	NR	5.3	NR	0	LVEF decline	NA
Hainsworth *et al.* [40]/II	RCC	55	Pazopanib 800 mg qd po q8w.	55	60	6	7.5	NR	1	LV dysfunction	NA
Kummar *et al.* [39]/II	STS	46	Cediranib 30 mg qd po q4w.	46	27	1.87	NR	NR	1	LV dysfunction	NA
Reynolds *et al.* [73]/II	NSCLC	63	Sunitinib 37.5 mg qd po q6w.	63	78.4	2.8	3	NR	0	CHF	NA

*Randomized controlled trial. †Data retrieved from drug package insert. §1200 mg m^{-2} in patients age ≥65 years. PFS, progression-free survival; TTP, time to progression; OS, overall survival; LVEF, left ventricular ejection fraction; CHF, congestive heart failure; RCC, renal cell cancer; STS, soft tissue sarcoma; MBC, metastatic breast cancer; NSCLC, non-small-cell lung carcinoma; GIST, gastrointestinal stromal tumours; CRC, colorectal cancer; HCC, hepatocellular carcinoma; PNET, pancreatic neuroendocrine tumours; NR, not reported; NA, not available. Qd daily; bid twice daily; q2w every 2 weeks; q3w every 3 weeks; q4w every 4 weeks; q6w every 6 weeks; q8w every 8 weeks.



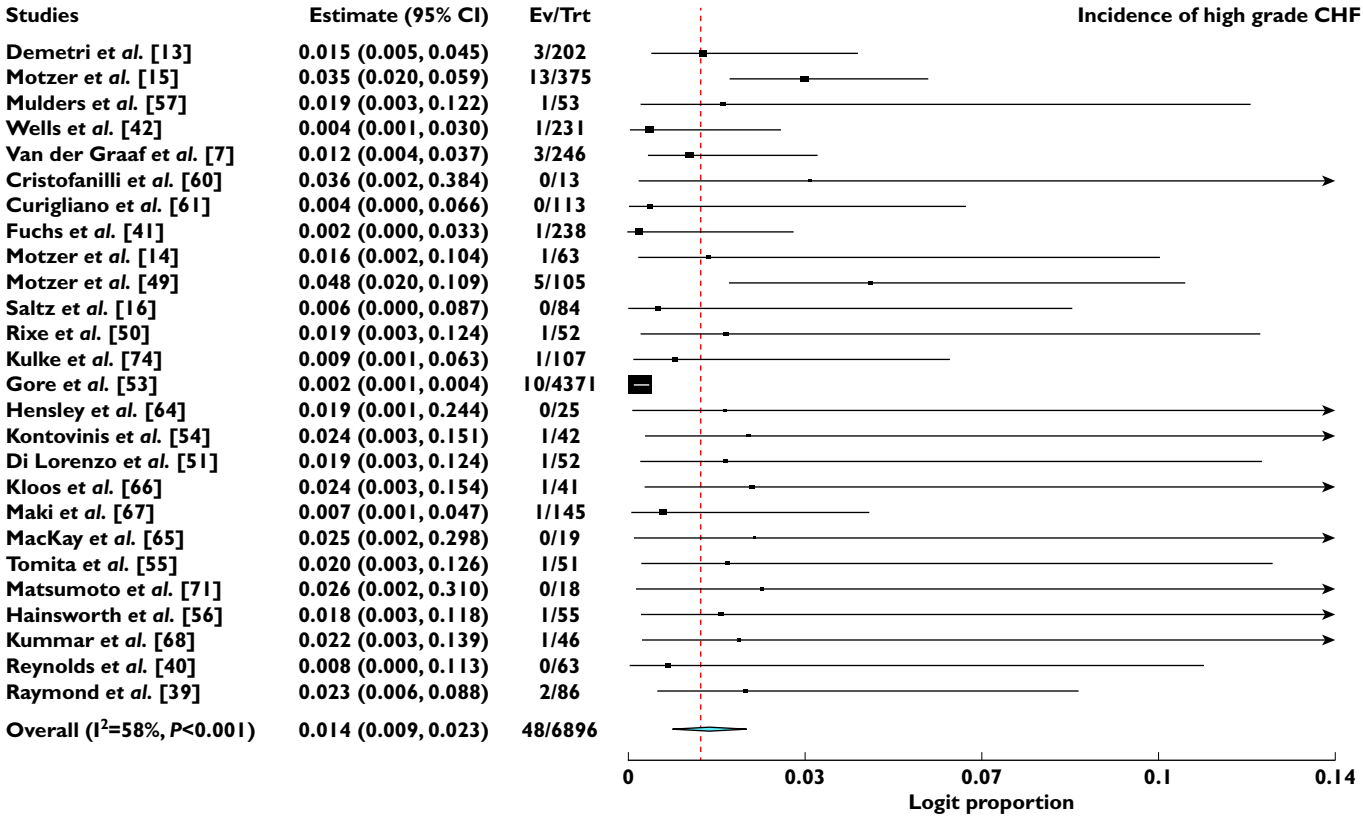


Figure 2

Incidence of all and high grade CHF associated with VEGFR-TKIs

Table 2
Incidence of CHF based on prespecified subgroups

Grades	Subgroup	Number of trials	CHF events	Total number of patients	I^2 (%)	Incidence (95% CI)	*P* for group difference
All grade	**Overall**	27	174	6903	90	3.2 (1.8, 5.8)	NA
	Tumour types						
	RCC	10	119	5228	96	4.5 (1.4, 13.6)	0.52
	Non-RCC	17	55	1675	63	3.0 (1.7, 5.1)	
	VEGFR-TKIs						
	Sunitinib	14	136	5638	94.3	3.6 (1.4, 8.8)	0.025
	Sorafenib	4	9	269	66.2	3.4 (0.9, 12.5)	
	Axitinib	2	3	114	0	2.7 (0.9, 8.1)	
	Cediranib	2	6	99	48.0	5.9 (1.5, 20.6)	
	Vandetanib	1	1	231	0	0.4 (0.1, 3.0)	
	Pazopanib	3	18	314	0	6.1 (3.9, 9.5)	
	Ramucirumab	1	1	238	0	0.4 (0.1, 2.9)	
	Phase of trials						
	Phase II	21	45	1240	32.8	4.5 (3.1, 6.6)	0.42
	Phase III	6	129	5663	97.8	2.4 (0.5, 10.2)	
High grade	**Overall**	26	48	6896	58	1.4 (0.9, 2.3)	NA
	Tumour types						
	RCC	10	35	5219	0	1.8 (0.7, 4.4)	0.55
	Non-RCC	16	13	1677	96	1.3 (0.8, 2.0)	
	VEGFR-TKIs						
	Sunitinib	15	37	5724	74.2	1.5 (0.7, 3.1)	0.72
	Sorafenib	3	3	238	0	1.5 (0.5, 4.5)	
	Axitinib	1	1	52	0	1.9 (0.3, 12.4)	
	Cediranib	2	2	99	0	2.0 (0.5, 7.7)	
	Vandetanib	1	1	231	0	0.4 (0.1, 3.0)	
	Pazopanib	3	4	314	0	1.5 (0.6, 3.7)	
	Ramucirumab	1	0	238	0	0	
	Phase of trials						
	Phase II	19	16	1147	97.4	2.1 (1.4, 3.3)	0.18
	Phase III	7	32	5749	0	0.9 (0.3, 2.8)	

RCC, renal cell carcinoma; NA, not available.

(0.4%), and there were significant variations in the incidence of all grade CHF among different VEGFR-TKIs ($P = 0.025$), but not for high grade CHF ($P = 0.72$).

Odds ratio of CHF

A meta-analysis of the OR for all grade CHF attributable to VEGFR-TKIs compared with controls was performed on 12 randomized controlled trials. The overall OR for all grade CHF was 2.37 (95% CI 1.76, 3.20, $P < 0.001$, Figure 3), according to the fixed effects model. As for high grade CHF, 15 RCTs were available for analysis. The combined OR also demonstrated that VEGFR-TKIs significantly increased the risk of developing CHF (OR = 3.51, 95% CI 1.74, 7.05, $P < 0.001$, Figure 3) using a fixed effects model. We also did a sensitivity analysis to examine the stability and reliability of pooled ORs by sequential omission of individual studies. The results indicated that the significance estimate of pooled all grade ORs was not significantly influenced by omitting any single study. As for high grade ORs, there was a non-significantly increased risk of developing high grade CHF after excluding the trial conducted by Motzer *et al.* [15] (Figure 4). Since in three studies, data on the length of treatment were not reported, nine of 12 studies were included in the analysis. The result indicated that the OR tended to be lower in the studies in which the experimental treatment was longer, and this effect was statistically significant ($\beta = 1.15$, $P = 0.13$, Figure 5). As for high grade CHF, a similar result was also observed ($\beta = 1.26$, $P = 0.52$, Figure 5). Based on these results, we believe that CHF might possibly occur early in treatment regimens.

Risk of CHF according to different tumour types, VEGFR-TKIs and phase of trials

To determine whether the observed increase in ORs of developing all and high grade CHF was the result of confounding bias, we preformed subgroup analyses of renal cell carcinoma (RCC) *vs.* other malignancies, phase II *vs.* phase III trials and trials with different VEGFR-TKIs. No significant differences were observed for ORs of all (1.91 *vs.* 3.36, $P = 0.071$) or high grade (3.02 *vs.* 4.31, $P = 0.72$) between patients with RCC and non-RCC. Similarly, no significant differences in ORs were found among different

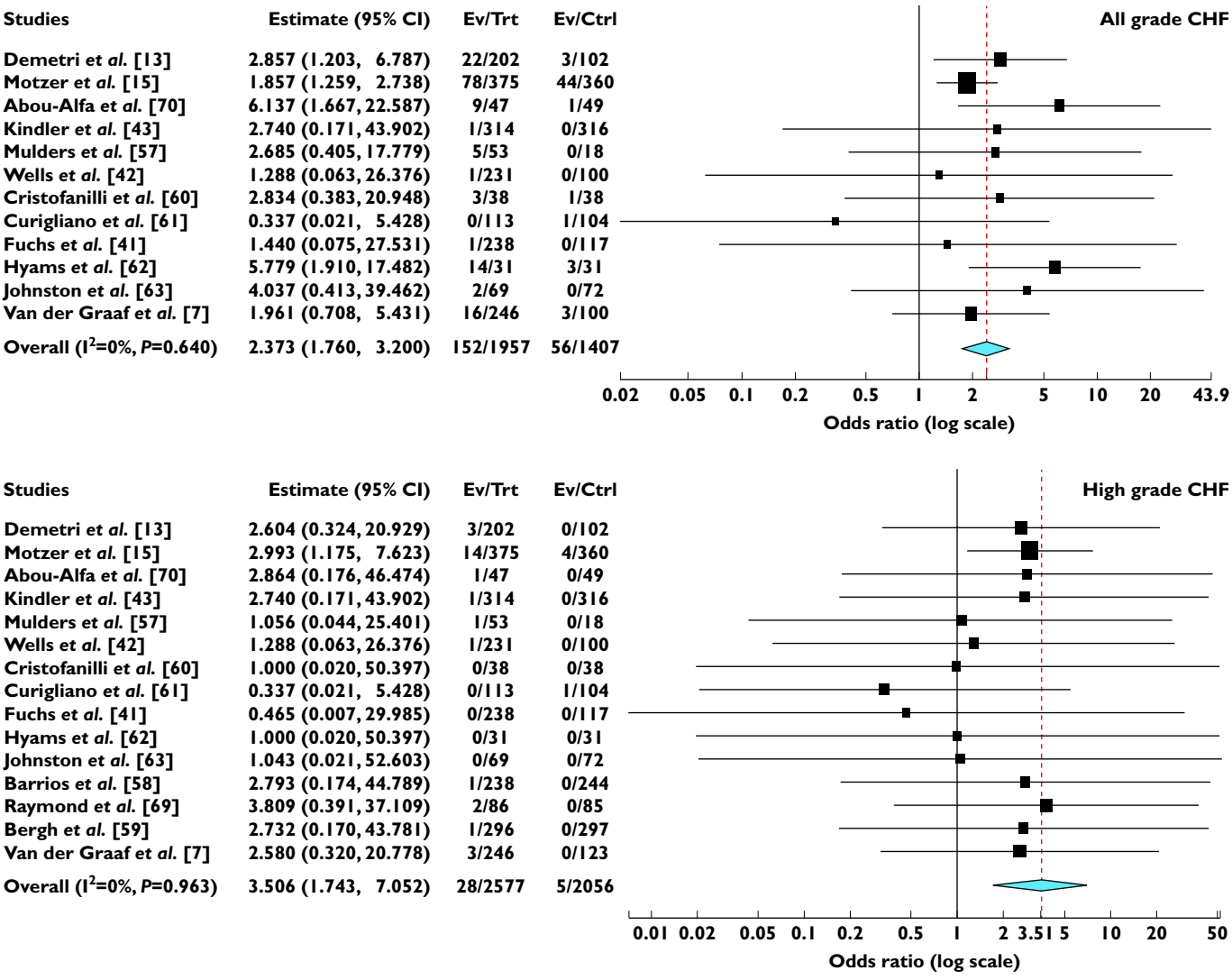


Figure 3

Odds ratio of all and high grade CHF associated with VEGFR-TKIs *vs.* control

VEGFR-TKIs (all grade: $P = 0.55$, high grade: $P = 0.99$, Table 3). Interestingly, the ORs of all grade CHF were significantly higher in phase II trials than in phase III trials (4.77 *vs.* 2.01, $P = 0.026$), but not for high grade CHF (2.21 *vs.* 3.73, $P = 0.67$).

Publication bias

No evidence of publication bias was detected for the OR of all grade and high grade ILD in this study by Egger's test (OR of all grade: $P = 0.18$, OR of high grade: $P = 0.66$).

Discussion

CHF is a rare but potentially life-threatening complication during anti-VEGF therapy [75, 76]. Concerns have arisen regarding the risk of CHF with the use of these drugs. A previous meta-analysis demonstrated that the incidence of high grade CHF was 1.6% (95% CI 1.0, 2.6%) among patients receiving the VEGF antibody bevacizumab, and patients treated with bevacizumab had a significantly increased risk of developing CHF (RR 4.74, 95% CI 1.66, 11.18, $P = 0.001$) [37]. However, the association between CHF and VEGFR-TKIs, which also target VEGF signalling pathways, has not been systematically defined. As a result, we conducted this study to investigate the overall incidence and risk of CHF in cancer patients treated with VEGFR-TKIs.

Our study included 10 553 patients from 36 clinical trials and demonstrated that the pooled incidence of VEGFR-TKIs associated all and high grade CHF was 3.2% (95% CI 1.8, 5.8%) and 1.4% (95% CI 0.9, 2.3%), respectively.

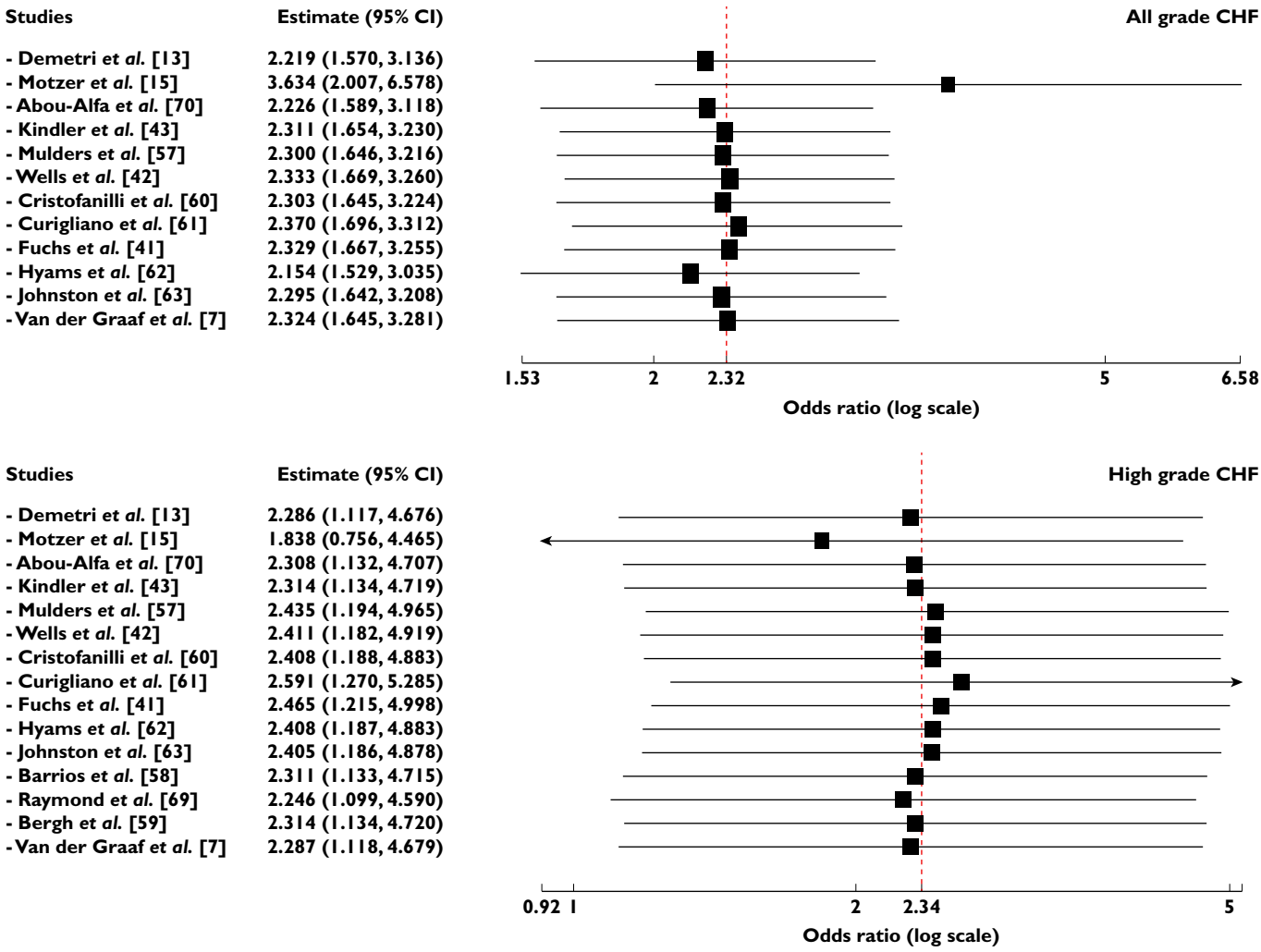


Figure 4

Meta-analysis of all and high grade CHF associated with VEGFR-TKIs *vs.* control: 'leave-one-out' sensitivity analysis

Additionally, we also found that the use of VEGFR-TKIs was associated with a significantly increased risk of all and high grade CHF when compared with controls. Sensitivity analysis indicated that the significance estimate of pooled all grade ORs was not significantly influenced by omitting any single study. As for high grade ORs, there is a non-significantly increased risk of developing high grade CHF after excluding the trial conducted by Motzer *et al*. [15]. In addition, the meta-regression indicated that the OR of CHF tended to be lower in studies in which the experimental treatment was longer, and the effect was statistically significant. Based on our findings, we could conclude that while VEGFR-TKIs are associated with an increased risk of developing CHF in cancer patients, the absolute incidence and risk of CHF appears low and the use of VEGFR-TKIs should be considered in the context of overall survival benefits. Moreover, as CHF commonly occurs early in the treatment with VEGFR-TKIs, close cardiac monitoring for patients receiving VEGFR-TKIs is recommended, especially during the initial of the regimens.

We also carried out a subgroup risk analysis stratified according to tumour type, VEGFR-TKIs agents, and phase of trials. Our results show that the incidence and risk of CHF associated with VEGFR-TKIs does not significantly vary with tumour types (all grade: $P = 0.071$, high grade $P = 0.72$). Then, we explored the incidence and risk of CHF among different VEGFR-TKIs. The incidence of CHF varied significantly with different VEGFR-TKIs ($P = 0.025$), reflecting the nature of the underlying tumour biology or the different spectrum of target receptors of VEGFR-TKIs. However, our study shows that the OR of CHF did not vary significantly with VEGFR-TKIs (all grade $P = 0.55$; high grade $P = 0.99$), but this is unclear with the sample size in this analysis. Additionally, we found that the risk of CHF was

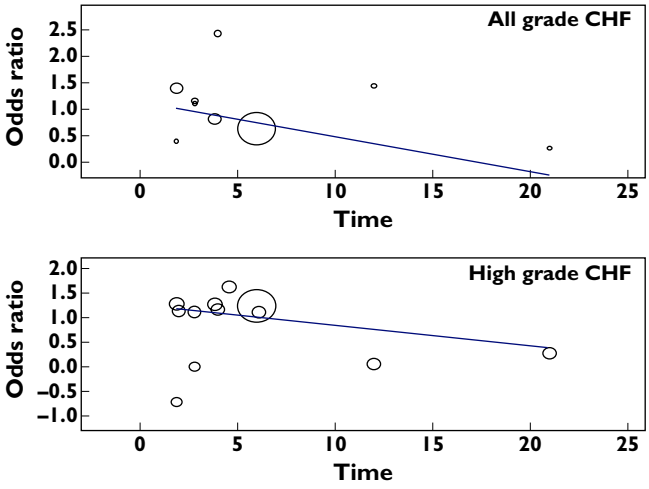


Figure 5

Meta-regression analysis of trends between treatment duration (months) and all and high grade odds ratio. Symbols: each study is represented by a circle the diameter of which is proportional to its statistical weight

substantially higher in phase II trials than that in phase III trials ($P = 0.026$), but not for high grade CHF ($P = 0.67$).

The pathogenesis of angiogenesis inhibitor related CHF is currently unknown, and multiple mechanisms might be involved in the pathogenesis of CHF. VEGFR-TKIs, such as sorafenib, sunitinib, vandetanib, pazopanib, axitinib and regorafenib, have been shown to increase the risk of hypertension. The RR for hypertension with these VEGF-TKIs has been shown to range between 1.71 and 8.06 [23, 25, 26, 30, 32, 33]. Hypertension is a well-known risk factor for development of CHF, and it is possible that VEGFR-TKIs use increases CHF through this mechanism [77]. Another potential mechanism of cardiotoxicity is through inhibition of the VEGF signal pathway. Inactivation of endogenous VEGF with an adenoviral vector encoding a decoy VEGFR could lead to a net reduction in capillary density, impaired cardiac hypertrophy and loss of contractile function after pressure overload in mice subjected to transverse aortic constriction [78], while microvascular plasticity allows adaptation of the vascular network, and thus oxygen supply to enhanced metabolic demand due to pressure overload [79]. Inhibiting the VEGF pathway blocks such plasticity, contributing to maladaptive hypertrophy of cardiomyocytes. Additionally, the platelet-derived growth factor (PDGF) signalling pathway also plays a crucial role in the heart. Inhibition of PDGFR-β in cardiomyocytes has been shown to induce heart failure in mice exposed to high vascular pressures [80].

Meta-analysis is considered as a useful tool for analyzing rare and unintended effects of a treatment because it could allow synthesis of data and achieve more stable estimates of effects. However, there are several limitations needed to be considered in our meta-analysis. First, these studies were conducted at various international institutions by different investigators and may have potential bias in reporting the types of adverse events. In particular, the frequency of CHF is under-reported in clinical trials. Second, although CHF events were prospectively collected for each individual study, this analysis was retrospective, and there are potentially important differences among the studies, including differing tumour types, dosage and administration schedule of VEGFR-TKIs, periods of study conduct and study investigators. All of these would increase the clinical heterogeneity among included trials, which also made the interpretation of a meta-analysis more problematic. Thirdly, VEGFR-TKI treatment has also been associated with a significant increase in the risk of hypertension and ATEs. Therefore, an increase in the risk of CHF may have been secondary to an increased incidence of hypertension and/or ATE [35]. However, we could not correlate the incidence of CHF with secondary hypertension or ATE, as neither the causality nor association was reported in any trial. In addition, we were not able to correlate our data with dose delays/interruptions or discontinuations secondary to CHF in the analysis. Fourthly, all these studies excluded patients with poor renal, haematological and hepatic function, and are performed mostly at major academic centres and research institutions. The analysis of these studies may not apply to patients with organ dysfunction and in the community, and the overall incidence and risk of CHF may be higher in medical practice. Finally, our study was a study-level meta-analysis and individual patient information was not available. Therefore, establishment of risk factors for the development of CHF, including prior exposure to cardiotoxic agents, or of potentially contributing comorbid conditions, including prior cardiovascular disease, was not possible in this analysis. Also, we could not determine the potential association between patients who developed CHF during VEGFR-TKIs treatment and efficacy of these drugs. Thus further studies are recommended to investigate this association.

In conclusion, our study suggests that the use of VEGFR-TKIs is associated with an increased risk of developing CHF. As these drugs are increasingly used in the routine treatment of cancer patients and in the setting of clinical trials in combination with other agents, physicians and investigators should be aware of this adverse effect and should monitor patients receiving VEGFR-TKIs closely to offer early intervention and to optimize the balance between oncologic clinical benefit and life-threatening adverse events.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and

Table 3

Odds ratio of CHF based on pre-specified subgroups

Grades	Subgroup	Number of trials	VEGFR-TKIs Events/total, *n*	Control Events/total, *n*	I^2 (%)	OR (95% CI)	*P* value	*P* for group difference
All grade	**Overall**	12	152/1957	56/1407	0	2.37 (1.76, 3.20)	<0.001	NA
	Tumour types							
	RCC	2	83/428	44/378	0	1.91 (1.30, 2.80)	0.001	0.071
	Non-RCC	10	69/1529	12/1029	0	3.36 (2.08, 5.43)	<0.001	
	VEGFR-TKIs							
	Sunitinib	3	100/690	48/566	26.0	1.95 (1.37, 2.78)	<0.001	0.55
	Sorafenib	1	9/47	1/49	0	6.14 (1.67, 22.59)	0.006	
	Axitinib	1	1/314	0/316	0	7.44 (0.15, 374.8)	0.32	
	Cediranib	2	19/84	3/49	0	5.37 (2.02, 14.3)	0.001	
	Vandetanib	1	1/231	0/100	0	4.19 (0.06, 299.27)	0.51	
	Pazopanib	3	21/353	4/210	0	2.40 (1.01, 5.69)	0.047	
	Ramucirumab	1	1/238	0/117	0	4.44 (0.07, 287.50)	0.48	
	Phase of trials							
	Phase II	7	34/665	6/628	0	4.77 (2.41, 9.43)	<0.001	0.026
	Phase III	5	118/1292	50/779	0	2.01 (1.44, 2.81)	<0.001	
High grade	**Overall**	15	28/2577	5/2056	0	3.51 (1.74, 7.05)	<0.001	NA
	Tumour types							
	RCC	2	15/428	4/378	0	3.02 (1.21, 7.55)	0.008	0.72
	Non-RCC	13	13/2149	1/1678	0	4.31 (1.46, 12.72)	0.018	
	VEGFR-TKIs							
	Sunitinib	6	21/1310	5/1192	0	3.19 (1.46, 6.95)	0.004	0.99
	Sorafenib	1	1/47	0/49	0	7.71 (0.15, 388.9)	0.31	
	Axitinib	1	1/314	0/316	0	7.44 (0.15, 374.8)	0.32	
	Cediranib	2	1/53	0/18	0	3.82 (0.04, 345.5)	0.56	
	Vandetanib	1	1/231	0/100	0	4.19 (0.06, 299.3)	0.51	
	Pazopanib	3	3/353	0/233	0	4.52 (0.41, 50.16)	0.22	
	Ramucirumab	1	0/238	0/117	0	NA	NA	
	Phase of trials							
	Phase II	7	3/665	1/628	0	2.21 (0.29, 16.72)	0.44	0.67
	Phase III	8	25/1912	4/1428	0	3.73 (1.77, 7.86)	<0.001	

RCC, renal cell carcinoma; NA, not available.

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