Systematic Review and Meta-Analysis

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Risk of regorafenib-induced cardiovascular events in patients with solid tumors

A systematic review and meta-analysis

Jianxin Chen, Master Degree[a], Junhui Wang, Master Degree[b,*]

Abstract

Background: The present comparative meta-analysis was conducted to evaluate the cardiovascular events of regorafenib in patients with solid tumors.

Methods: Eligible studies from MEDLINE, Google Scholar, Cochrane Library, Clinical key, EBSCO publishing and Ovid, which had reported cardiovascular adverse events potentially caused by regorafenib were absorbed. Data of clinical characteristics and cardiovascular events including hypertension, hemorrhage, thrombosis, and heart failure were extracted from selected literatures for the final analysis. Pooled analysis of cardiovascular adverse events was developed by relative risks (RRs) and corresponding 95% confidence intervals (CIs) with software STATA 13.0 and RevMan 5.3.

Results: Thirty studies including 3813 patients were fit into analysis. The incidences of cardiovascular events of all-grade were: hypertension, 36.8% (95% CI, 29.8%–43.8%), hemorrhage, 8.6% (95% CI, 3.2%–14%), thrombosis, 1.4% (95% CI, 0.1%–2.8%), and heart failure, 2.9% (95% CI, 0.3%–5.6%). The incidences of cardiovascular events of high-grade were: hypertension, 9.9% (95% CI, 7.4%–12.4%), hemorrhage, 1.2% (95% CI, 0.3%–2.2%), thrombosis, 1.6% (95% CI, 0.2%–3.4%), and heart failure, 2.9% (95% CI, 0.3%–5.6%). The RRs and their 95% CIs of all-grade cardiovascular events among patients treated with regorafenib were: hypertension, 4.10 (95% CI, 3.07–5.46; $P < .00001$), hemorrhage, 2.71 (95% CI, 1.45–5.08; $P = .002$), thrombosis, 1.27 (95% CI, 0.49–3.27; $P = .62$), and heart failure, 0.79 (95% CI, 0.16–3.94; $P = .77$). The RRs and their 95% CIs of high-grade cardiovascular events among patients treated with regorafenib were: hypertension, 5.82 (95% CI, 3.46–9.78; $P < .00001$), hemorrhage, 0.90 (95% CI, 0.50–1.61; $P = .72$), thrombosis, 1.28 (95% CI, 0.48–3.41; $P = .62$), and heart failure, 1.15 (95% CI, 0.23–5.69; $P = .86$), respectively.

Conclusion: The present meta-analysis has demonstrated that regorafenib is associated with an increasing risk of hypertension at all-grade and high-grade, as well as hemorrhage at all-grade. Adequate awareness of cardiovascular adverse events of regorafenib should be established for clinicians.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitors, aGC = advanced gastric cancer, AM = America, aSTS = advanced soft tissue sarcoma, CHP = congestive heart failure, CI = confidence intervals, DBP = diastolic blood pressure, ECOG PS = European cooperative oncology group performance status, FGFR = fibroblast growth factor receptor, FLT1 = fms-related tyrosine kinase 1, GIST = gastrointestinal stromal tumor, HCC = hepatocellular carcinoma, ICH = intracranial hemorrhage, KDR = kinase insert domain receptor, LVEF = left ventricular ejection fraction, mCRC = metastatic colorectal cancer, NCI CTC = National Cancer Institute Common Toxicity Criteria, NR = not reported, PDGFR = platelet-derived growth factor, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PTK = protein tyrosine kinase, RC = renal carcinoma, Reg = regorafenib, RR = relative risk, SBP = systemic blood pressure, STs = solid tumors, TKI = tyrosine kinase inhibitors, VEGFR = vascular endothelial growth factor receptor.

Keywords: cardiovascular events, meta-analysis, regorafenib, solid tumors

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[a] *Department of Medical Oncology,* [b] *Department of Radiation Oncology, Quzhou People's Hospital, Quzhou, Zhejiang, China.*

[*] *Correspondence: Junhui Wang, Department of Radiation Oncology, Quzhou People's Hospital, Quzhou, 324000, Zhejiang, China (e-mail: wangjunhui7526@163.com).*

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1. Introduction

Regorafenib, also known as Stivarga or BAY 73-4506, an oral small molecule multi-kinase inhibitor, has emerged as a targeted agent which inhibit the activity of various kinase, including fms-related tyrosine kinase 1 (FLT1, also known as vascular endothelial growth factor receptor 1,VEGFR1), kinase insert domain receptor (KDR, also known as VEGFR2), FLT4 (VEGFR3), platelet-derived growth factor α (PDGFR-α), PDGFR-β, KIT proto-oncogene receptor tyrosine kinase, fibroblast growth factor receptor 1 (FGFR1), FGFR2, TEK receptor tyrosine kinase, RAF-1, tyrosine-protein kinase TIE-2, v-RAF murine sarcoma viral oncogene homolog B (BRAF), $BRAF^{V600E}$, stress-activated protein kinase 2 (SAPK2), and protein tyrosine kinase 5 (PTK5).[1,2] With the positive results of several related clinical trials, regorafenib has been approved by the United States Food and Drug Administration (FDA) for the therapy of metastatic colorectal carcinoma (mCRC),[3] advanced gastrointestinal stromal tumors (GIST),[4] and hepatocellular carcinoma (HCC).[5]

However, like other VEGFR tyrosine kinase inhibitors (TKIs), most of the randomized clinical trials on regorafenib were focus primarily on its anti-tumor efficacy, which might be more beneficial for its approval by administration, rather than cardiovascular events, which were reported as secondary outcomes.[3–8] That makes a precise definition of the complete spectrum of adverse events challenging. In addition, owing to the low incidence rate of cardiovascular events in one research, the specific types of events, incidence rate, relative risk to placebo, and potential influence on the management during the treatment of carcinoma still remain elusive.[9,10]

Thus, to provide some suggestion for clinicians, as well as onco-cardiology patients, the present systematic review and meta-analysis was performed to evaluate the incidence rate and relative risk (RR) of cardiovascular events induced by regorafenib in patients with solid carcinomas among available clinical trials.

2. Methods

2.1. Literature search

A literature review among databases including MEDLINE, Google Scholar, Cochrane Library, Clinical key, EBSCO publishing, and Ovidwas conducted up to November 2017 with the main key word regorafenib. The search was limited to clinical trials including perspective or prospective ones, which published in English. The present meta-analysis was conducted in compliance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[11]

2.2. Inclusion and exclusion criteria

Inclusion criteria: Clinical trials related to regorafenib in patients with solid tumors; participants were suggested to receive regorafenib or placebo treatment in controlled studies or regorafenib alone in single-armed studies; adverse events at all-grade or high-grade of hypertension, hemorrhage, thrombosis, or heart failure were reported. Exclusion criteria: publications of review articles, case reports, correspondences, and basic researches were excluded; meeting abstracts without data of cardiovascular event reported; classification of adverse event did not meet the standard of National Cancer Institute Common Toxicity Criteria (NCI CTC).

2.3. Data extraction

Data extraction was performed by 2 independent investigator. The following information was extracted from each included literature: first author's name, year of publication, region, cancer sites, previous treatment lines, number of patients, median age, sex, European cooperative oncology group performance status (ECOG PS), median treatment duration, and the dose of regorafenib. In terms to cardiovascular events, adverse events including hypertension, hemorrhage, thrombosis, and heart failure at all-grade and high-grade were recorded according to NCI CTC versions. Any discrepancies between investigators were resolved by consensus.

2.4. Quality assessment of included studies

The quality of the included randomized clinical trials (RCTs) was evaluated with the criteria of Cochrane Collaboration's tool for assessing risk of bias of RCTs by the 2 reviewers. The following items were adopted for the assessment: random sequence generation, allocation concealment, binding of participants and personnel, binding of outcome assessments, incomplete outcome data, selective reporting and other bias, which were presented with figures, such as "risk of bias graph" and "risk of bias summary."

2.5. Statistical analysis

The primary objective of the present study was to investigate the incidence rate, RR, and corresponding 95% confidence intervals (CIs) of cardiovascular events at all-grade and high-grade of regorafenib in patients with solid tumors. For the calculation of incidence rate, data of the number of patients, as well as the number of cardiovascular events at all-grade and high-grade, were extracted from all the selected literatures, including randomized, controlled trials, and single-armed researches. Non-comparative binary data were analyzed as follows. $P = X/n$; $SE(P) = (P[1-P)/n)^{1/2}$ (P, incidence rate; X, events; n, total; SE, standard error). The formulas were appropriate for the circumstance of approximate normal distribution of sampling. If the data were unmatched to normal distribution, the formulas were adopted as follows, $P = \ln(X/[n-X])$; $SE(P) = (1/X + 1/[n-X])^{1/2}$; $Pt = OR/(1+OR)$; 95%CI lower limit, $LL = LL_{OR}/(1+LL_{OR})$; 95%CI upper limit, $UL = UL_{OR}/(1+UL_{OR})$. The incidences of cardiovascular events were performed with software STATA 13.0 (StataCorp LP, Texas). For the analysis of RR, data of number of patients and the ones of cardiovascular events at all-grade and high-grade were extracted from randomized, placebo-controlled trials only. Cochrane Q test and inconsistency statistic (I^2) were applied for the heterogeneity evaluation among the included literatures. The calculations of RR were developed with software RevMan 5.3 (Cochrane Collaboration, USA). P-value $>.1$ and $I^2 < 50\%$ were supposed to show no substantial heterogeneity existed. Random effect model or fixed effect one were applied for the analysis of data of heterogeneous or not for both incidence and RR. A P-value $<.05$ was considered statistically significant. Potential publication bias was detected with funnel plots in software RevMan 5.3.

3. Results

3.1. Search results

A total of 884 potential literatures has been initially searched in databases including MEDLINE, Google Scholar, Cochrane

Library, Clinical key, EBSCO Publishing and Ovid. Five hundred twenty articles were removed because of duplications. Two hundred fourty-six researches were further excluded with the property of clinical trials in regard to regorafenib. With the inclusion criteria, 34 papers were adsorbed for the potentially final assessment. After full text carefully reviewed, 4 researches had been conclusively eliminated because of reasons including insufficient data of cardiovascular events (n=2), confusing classification of events (n=1), and therapeutic drugs rather than placebo or blank as control (n=1). Accordingly, a total of 30 clinical trials related to regorafenib were considered eligible for the final analysis. Six studies were placebo-controlled prospective clinical trials, and the other 24 researches were single-armed trials. A flow diagram which detailed the selection of included studies was presented in Fig. 1.

3.2. Quality assessment of the included studies

With the performance of quality evaluation within the criteria of Cochrane Collaboration's tool for assessing risk of bias of RCTs, we found that all the included RCTs satisfied the items including random sequence generation, allocation concealment, binding of participants and personnel, and binding of outcome assessments. However, cardiovascular events such as hypertension, hemorrhage, thrombosis, or heart failure were not entirely reported in selective literatures, results of which were presented in Figs. 2 and 3.

3.3. Population characteristics

A total of 3813 patients were considered available in the present meta-analysis, solid tumors of which included GIST, mCRC, advanced gastric cancer (aGC), HCC, advanced soft tissue sarcoma (aSTS), and renal carcinoma (RC). The majority of

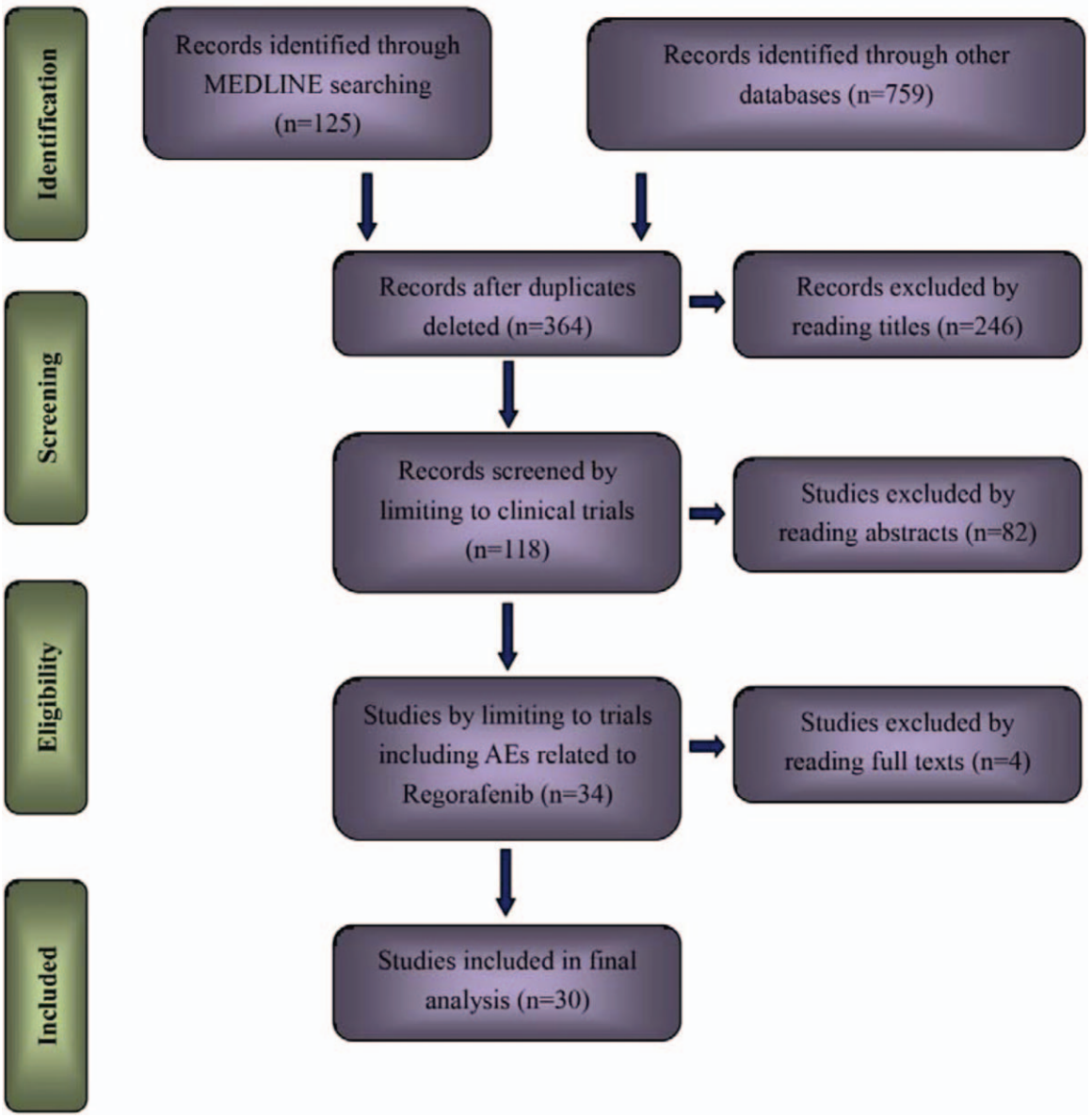

Figure 1. Study selection procedure with PRISMA flow diagram. PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

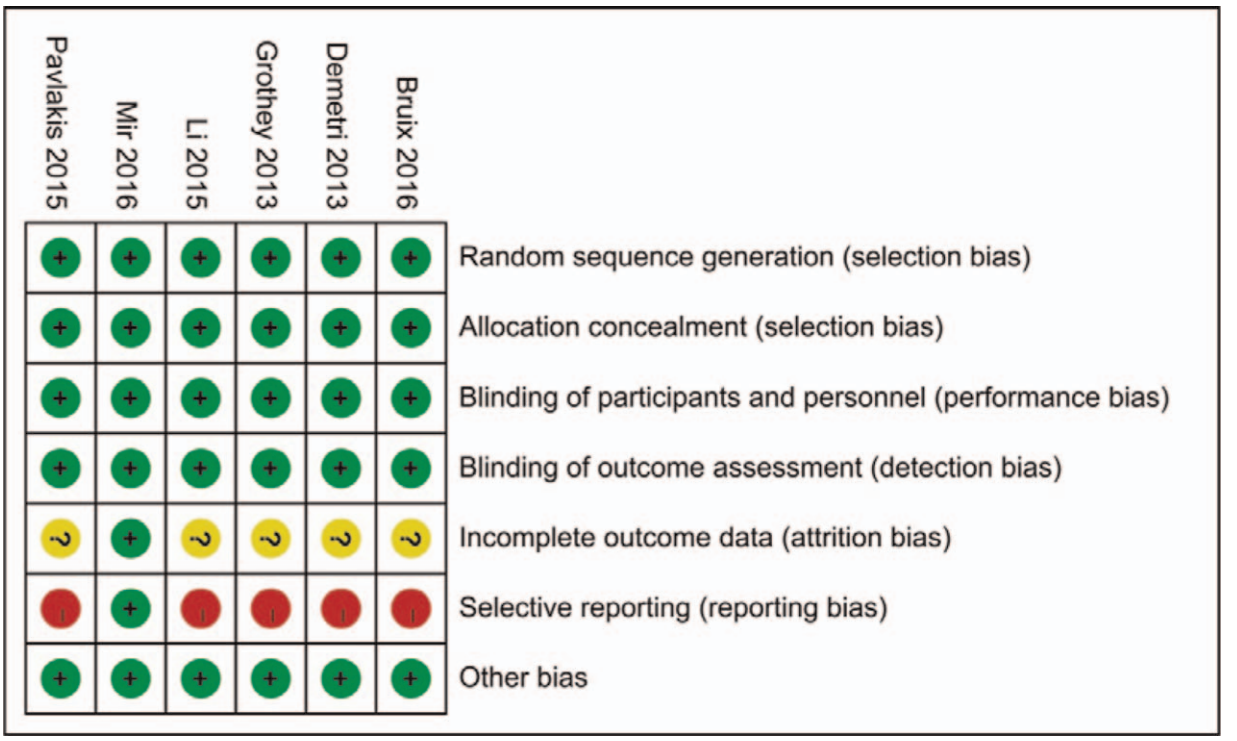

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

patients have Eastern Cooperative Oncology Group performance status (ECOG PS) as 0, 1, and 2. The baseline clinic-pathological characteristics and the number of cardiovascular events of all-grade and high-grade in all included researches were presented in Tables 1 and 2.

3.4. Overall incidence of cardiovascular events

All the including researches were pooled analyzed for the overall incidence of cardiovascular events. The incidences of all-grade cardiovascular events were: hypertension, 36.8% (95% CI, 29.8%–43.8%), hemorrhage, 8.6% (95% CI, 3.2%–14%), thrombosis, 1.4% (95% CI, 0.1%–2.8%), and heart failure, 2.9% (95% CI, 0.3%–5.6%). The incidence of high-grade cardiovascular events were: hypertension, 9.9% (95% CI, 7.4%–12.4%), hemorrhage, 1.2% (95% CI, 0.3%–2.2%), thrombosis, 1.6% (95% CI, 0.2%–3.4%), and heart failure, 2.9% (95% CI, 0.3%–5.6%). Random-effects models were adopted for the pooled analysis of hypertension, hemorrhage, and thrombosis due to the significant heterogeneities for the events of all-grade and high-grade, while fixed-effects model explored for event of heart failure at all-grade and high-grade because of the insignificant heterogeneities, forest plots of which were showed in appendix 1–8, http://links.lww.com/MD/C556 (see figure 1–8, Supplemental Digital Content, which present the forest plots of

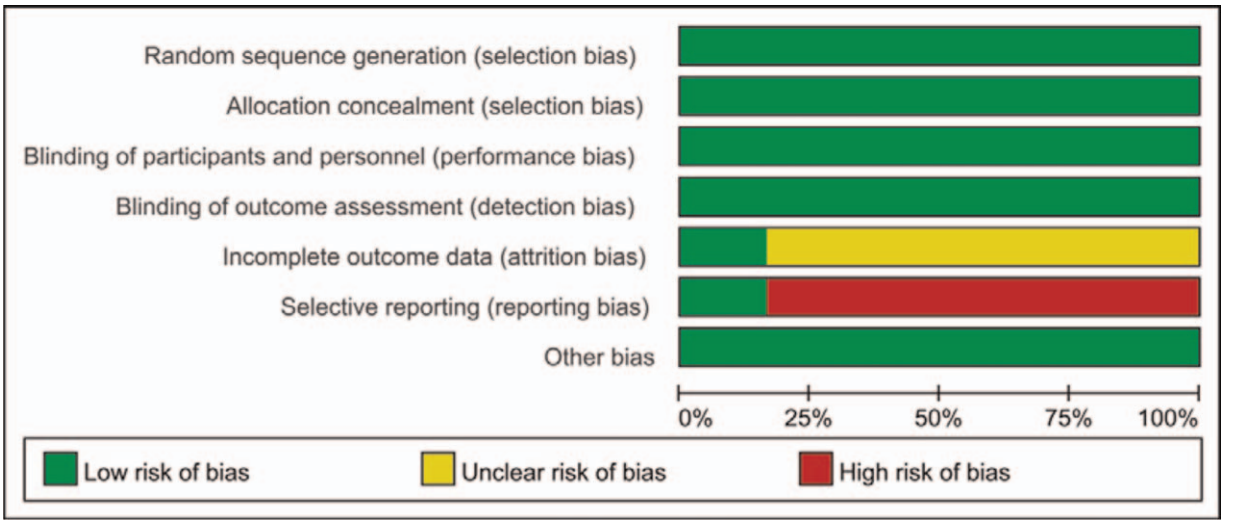

Figure 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages among all included studies.

Table 1

Baseline characteristics of the researches included in present study.

Author (year)	Region	Cancer sites	Previous lines	No. of patients	Gender (male/female)	Median age (range), year	ECOG (PS, 0/1/2)	Treatment duration, median (range), month	Dose of Reg. (mg)
Demetri 2013	Globe	GIST	≥2	199 Arm I:133 Arm II:66	Arm I:85/48 Arm II:42/24	Arm I:60 (51–67) Arm II 61 (48–66)	Arm I:73/60 Arm II:37/29	ArmI:5.3 (2.2–6.7) Arm II:1.6 (1.2–2.6)	ArmI:160 Arm II:160
Li 2015	Asian	mCRC	≥2	204 Arm I: 136 Arm II:68	Arm I:85/51 Arm II:33/35	ArmI:57.5 (50–66) Arm II 55.5 (48.5–62)	ArmI:35/101 Arm II:15/53	ArmI:2.4 (1.6–5.3) Arm II:1.6 (1.1–1.6)	ArmI:160 Arm II:160
Grothey 2013	Globe	mCRC	≥1	760 Arm I: 505 Arm II:255	Arm I:311/194 Arm II:153/102	Arm I:61 (54–67) Arm II:61 (54–68)	ArmI:265/240 Arm II:146/109	ArmI:1.7 (1.4–3.7) Arm II:1.6 (1.3–1.7)	ArmI:160 Arm II:160
Pavlakis 2015	Globe	aGC	≥1	147 Arm I: 97 Arm II:50	Arm I:78/19 Arm II:40/10	ArmI:63 (33–81) Arm II:62 (32–85)	Arm I:41/56 Arm II:21/29	ArmI:1.8 (1.4–2.0) Arm II:0.9 (0.9–1.0)	ArmI:160 Arm II:160
Bruix 2016	Globe	HCC	≥1	573 Arm I: 379 Arm II:194	Arm I:333/46 Arm II:171/23	Arm I:64 (54–71) Arm II:62 (55–68)	ArmI:247/132 Arm II:130/64	Arm I:3.6 (1.6–7.6) Arm II:1.9 (1.4–3.9)	ArmI:160 Arm II:160
Mir 2016	Europe	aSTS	≥1	182 Arm I: 90 Arm II:92	Arm I:43/47 Arm II:49/43	Arm I:57 (24–76) Arm II:65 (22–80) Arm I:60 (37–74) Arm II:60 (30–76) Arm I:46 (21–73) Arm II:35 (20–68) Arm I:60 (26–81) Arm II:55 (20–78)	ArmI:41/49/0 Arm II:45/46/1	ArmI:1.6 (0.7–2.4) Arm II:1.9 (1.6–4.8) ArmI:3.9 (2.0–8.7) Arm II:2.3 (1.6–4.6) ArmI:3.4 (0.7–6.7) Arm II:1.4 (0.7–2.0) ArmI:3.5 (0.6–10.2) Arm II:2.8 (1.1–5.1)	ArmI:160 ArmII:160 ArmI:160 Arm II:160
Yeh 2017	Asian	GIST	≥1	18	12/4	59 (36–71)	6/12	10 (0.6–24.9)	120
Son 2016	Asian	GIST	≥2	57	34/23	56 (50–62)	0/52/5	4.7 (0.9–27.1)	160
Schvartsman 2017	AM	GIST	≥2	28	17/11	58 (21–84)	NR	7.3 (0.9–18.8)	120
Osawa 2016	Asian	mCRC	≥2	20	14/6	65.5 (40–76)	3/14/3	1.9 (0.9–8.4)	160/120
Lam 2016	Asian	mCRC	≥0	45	32/13	63 (45–80)	41*/4	1.0**	160/120
Adenis 2016	Europe	mCRC	≥1	654	NR	64 (25–91)	200/383/60	2.2 (0.1–20.5)	160/120/80/40
Kopeckova 2016	Europe	mCRC	≥1	146	93/53	60.1 (25–81)	47/89/3	3.6 (0.3–9.4)	160/120/80
Komori 2017	Asian	mCRC	≥1	146	90/56	64 (37–87)	41/92/13	NR	160
Kakizawa 2016	Asian	mCRC	≥1	20	13/7	67.5 (49–76)	18*/2	NR	160/120/80/40
Gotfrit 2017	Europe	mCRC	≥1	35	20/15	61 (37–84)	14/20/1	NR	160/120/80
Prete 2017	Europe	mCRC	≥1	136	92/44	57 (31–79)	104*/32	3.5**	160/120/80
Cicero 2018	Europe	mCRC	≥2	60	38/22	58 (30–80)	60*	NR	160
Zanwar 2016	Asian	mCRC	≥2	23	12/11	50	2/15/6	3.8**	160/120
Sueda 2016	Asian	mCRC	≥2	23	12/11	59 (37–83)	10/13	2.3 (0.1–14.7)	160
Calcagno 2016	Europe	mCRC	≥2	29	NR	68 (40–83)	7/18/4	2.5 (0.13–11.4)	160/120/80
Kim 2015	Asian	mCRC	≥1	32	20/12	57 (29–79)	31*/1	NR	160
Hirano 2015	Asian	mCRC	≥2	32	18/14	61 (30–78)	8/21/3	2.5 (0.1–12.0)	160
Sunakawa 2014	Asian	STs	≥0	15	11/4	59 (34–68)	12/3	2.1 (0.9–20.1)	160
Kollar 2014	Europe	GIST	≥2	20	13/7	68 (45–87)	18*/2	9.25 (0.1–15.33)	160/120/80
Bruix 2013	Europe	HCC	≥1	36	32/4	61 (40–76)	28/8	4.55 (0.47–24.03)	160/120/80
Strumberg 2012	Europe	mCRC	≥0	38	21/17	64 (36–85)	18/18/2	1.77 (0.23–9.33)	220/160/120/60
Mross 2012	Europe	STs	≥0	53	30/23	60 (20–77)	26/25/2	2.6 (0.1–41.3)	220/160/120/60/30/10
George 2011	AM	GIST	≥2	33	19/14	56 (25–76)	23/10	NR	160
Eisen 2012	Europe	RC	≥0	49	27/22	62 (53–68)	30/19	7.1 (0.7–34.4)	160

aGC = advanced gastric cancer, AM = America, aSTS = advanced soft tissue sarcoma, ECOG PS = European cooperative oncology group performance status, GIST = gastrointestinal stromal tumor, HCC = hepatocellular carcinoma, mCRC = metastatic colorectal cancer, NR = not reported, RC = renal carcinoma, Reg = Regorafenib, STs = solid tumors.

* Including PS = 0 or 1.

** Mean duration of treatment.

Table 2

Number of events reported in included literatures.

Author (year)	Cancer sites	Number of patients	Events of hypertension		Events of hemorrhage		Events of thrombosis		Events of heart failure		CTC AE version
			All-grade	High-grade	All-grade	High-grade	All-grade	High-grade	All-grade	High-grade	
Demetri 2013	GIST	199 Arm I: 133 Arm II:66	Arm I:64 Arm II:11	Arm I:31 Arm II:2	NR	NR	NR	NR	NR	NR	4.0
Li 2015	mCRC	204 Arm I: 136 Arm II:68	Arm I:31 Arm II:3	Arm I:15 Arm II:2	Arm I:1 Arm II:0	Arm I:1 Arm II:0	NR	NR	Arm I:0 Arm II:1	Arm I:0 Arm II:1	4.0
Grothey 2013	mCRC	760 Arm I: 505 Arm II:255	Arm I:139 Arm II:15	Arm I:36 Arm II:2	Arm I:38 Arm II:5	Arm I:2 Arm II:0	Arm I:12 Arm II:4	Arm I:12 Arm II:4	NR	NR	3.0
Pavlakis 2015	aGC	147 Arm I: 97 Arm II:50	NR	Arm I:10 Arm II:1	NR	NR	NR	NR	NR	NR	4.0
Bruix 2016	HCC	573 Arm I: 379 Arm II:194	Arm I:87 Arm II:9	Arm I:49 Arm II:6	NR	Arm I:21 Arm II:15	Arm I:1 Arm II:0	Arm I:1 Arm II:0	NR	NR	4.03
Mir 2016	aSTS	182 Arm I: 90 Arm II:92	Arm I:32 Arm II:10	Arm I:17 Arm II:2	Arm I:12 Arm II:7	Arm I:2 Arm II:0	Arm I:1 Arm II:2	Arm I:0 Arm II:1	Arm I:2 Arm II:1	Arm I:2 Arm II:0	4.03
Yeh 2017	GIST	18	16	5	NR	NR	NR	NR	NR	NR	4.0
Son 2016	GIST	57	16	4	NR	NR	NR	NR	NR	NR	4.0
Schvartsman 2017	GIST	28	7	2	NR	NR	NR	NR	NR	NR	4.0
Osawa 2016	mCRC	20	4	1	1	1	NR	NR	NR	NR	4.0
Lam 2016	mCRC	45	20	4	13	1	NR	NR	NR	NR	4.0
Adenis 2016	mCRC	654	72	30	NR	1	NR	NR	NR	NR	4.0
Kopeckova 2016	mCRC	146	NR	1	NR	NR	NR	NR	NR	NR	3.0
Komori 2017	mCRC	146	76	14	NR	NR	NR	NR	NR	NR	4.0
Kakizawa 2016	mCRC	20	15	0	NR	NR	NR	NR	NR	NR	4.0
Gotfrit 2017	mCRC	35	11	2	NR	NR	NR	NR	NR	NR	NR
Prete 2017	mCRC	136	75	20	NR	NR	NR	NR	NR	NR	4.03
Cicero 2018	mCRC	60	15	NR	NR	NR	NR	NR	NR	NR	4.0
Zanwar 2016	mCRC	23	11	5	NR	NR	NR	NR	NR	NR	4.03
Sueda 2016	mCRC	23	11	1	NR	NR	NR	NR	NR	NR	4.0
Calcagno 2016	mCRC	29	1	0	2	1	NR	NR	1	1	4.01
Kim 2015	mCRC	32	NR	NR	NR	NR	NR	NR	3	3	3.0
Hirano 2015	mCRC	32	15	3	NR	NR	NR	NR	NR	NR	4.0
Sunakawa 2014	STs	15	5	0	NR	NR	NR	NR	NR	NR	3.0
Kollar 2014	GIST	20	10	3	NR	NR	NR	NR	NR	NR	4.0
Bruix 2013	HCC	36	13	1	NR	NR	NR	NR	NR	NR	3.0
Strumberg 2012	mCRC	38	7	4	NR	NR	NR	NR	NR	NR	3.0
Mross 2012	STs	53	16	6	NR	NR	NR	NR	NR	NR	3.0
George 2011	GIST	33	NR	12	NR	NR	NR	1	NR	NR	4.0
Eisen 2012	RC	49	24	3	NR	NR	NR	NR	NR	NR	NR

aGC = advanced gastric cancer, aSTS = advanced soft tissue sarcoma, CTC AE = common terminology criteria for adverse events, GIST = gastrointestinal stromal tumor, HCC = hepatocellular carcinoma, mCRC = metastatic colorectal cancer, NR = not reported, RC = renal carcinoma, STs = solid tumors.

adverse events including hypertension, hemorrhage, thrombosis, and heart failure at all/high grade).

3.5. Relative risk of cardiovascular events

A meta-analysis of the RRs of cardiovascular events at all-grade and high-grade were performed in the 6 randomized, placebo-controlled clinical trials. Thus, a total of 2065 patients were enrolled. The RRs and their 95% CIs of all-grade cardiovascular events were: hypertension, 4.10 (95% CI, 3.07–5.46; $P < .00001$), hemorrhage, 2.71 (95% CI, 1.45–5.08; $P = .002$), thrombosis, 1.27 (95% CI, 0.49–3.27; $P = .62$), and heart failure, 0.79 (95% CI, 0.16–3.94; $P = .77$). The RRs and their 95% CIs of high-grade cardiovascular events were: hypertension, 5.82 (95% CI, 3.46–9.78; $P < .00001$), hemorrhage, 0.90 (95% CI, 0.50–1.61; $P = .72$), thrombosis, 1.28 (95% CI, 0.48–3.41; $P = .62$), and heart failure, 1.15 (95% CI, 0.23–5.69; $P = .86$), respectively (Figs. 4A–D and 5A–D).

3.6. Publication bias

Funnel plot analysis has revealed no evidence of a publication bias for RRs of cardiovascular events at all-grade or high-grade (appendix 9–16, http://links.lww.com/MD/C556, see figure 9–16, Supplemental Digital Content, which present the funnel plots of hypertension, hemorrhage, thrombosis, and heart failure at all/high grade at all/high grade for publication bias).

4. Discussion

To the best of our knowledge, here is the most updated and largest scaled systematic review and meta-analysis to evaluate the

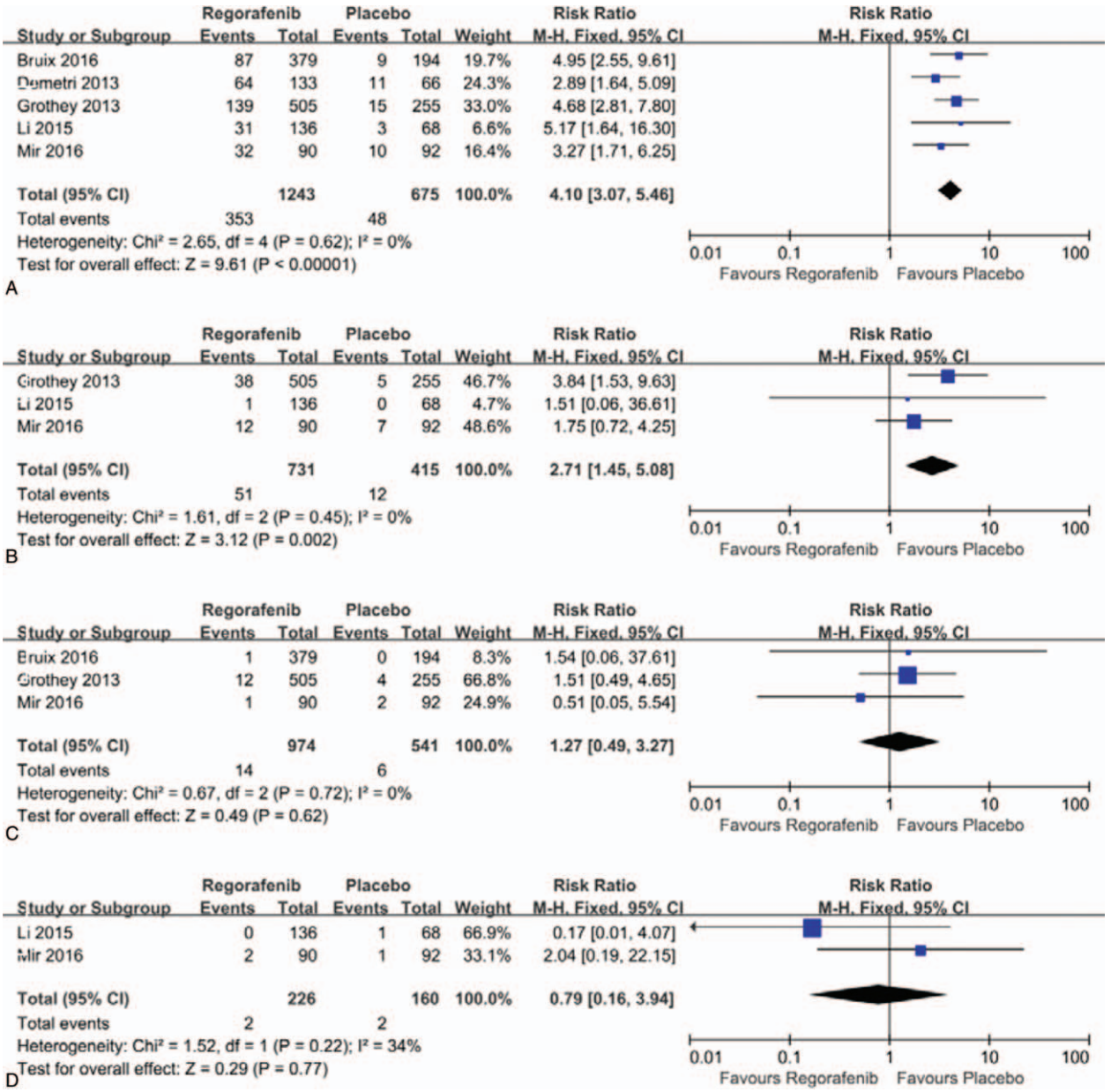

Figure 4. (A–D). Forest plots of relative risk of cardiovascular events of all-grade associated with regorafenib versus control. A. Hypertension; B. Hemorrhage; C. Thrombosis; D. Heart failure.

incidence and RR of the cardiovascular events for regorafenib in patients with solid carcinomas. Our analysis of available data revealed the incidence of cardiovascular events at all-grade and high-grade (grade 3 and 4) related to regorafenib were: hypertension at all-grade, 36.8% (95% CI, 29.8%–43.8%), and hypertension at high-grade, 9.9% (95% CI, 7.4%–12.4%); hemorrhage at all-grade, 8.6% (95% CI, 3.2%–14%), and hemorrhage at high-grade, 1.2% (95% CI, 0.3%–2.2%); thrombosis at all-grade, 1.4% (95% CI, 0.1%–2.8%), and thrombosis at high-grade, 1.6% (95% CI, 0.2%–3.4%); heart failure at all-grade, 2.9% (95% CI, 0.3%–5.6%), and heart failure at high-grade, 2.9% (95% CI, 0.3%–5.6%). Additionally, the present analysis demonstrated a significantly increased risk of hypertension at all-grade and high-grade, as well as hemorrhage at all-grade with the treatment of regorafenib compared with control.

With the extension of treatment duration and survival time, antitumor-induced cardiotoxicity has emerged as the second cause of death in patients who had received antitumor therapy.[12] Approximately, 2% to 3% patients had been reported suffering antitumor-induced cardiotoxicities during treatment in perspective clinical trials, while nearly 26% of which in prospective ones accounted.[13] A majority of cytotoxic agents have already been revealed with substantial cardiovascular events, such as adriamycin,[14] cyclophosphamide,[15] cisplatin,[16] fluorouracil,[17,18] and paclitaxel,[19] among which adriamycin comes to be the most outstanding one. The widely accepted hypothesis for adriamycin-induced cardiotoxicity were the generation of excess reactive oxygen species (ROS),[20] Topoisomerase (Top) 2β inhibition,[21] and the activation of p53 with its apoptotic pathway.[22] As the clinical application for decades with those agents, sufficient attention for cardiovascular toxicity has been paid, and relevant

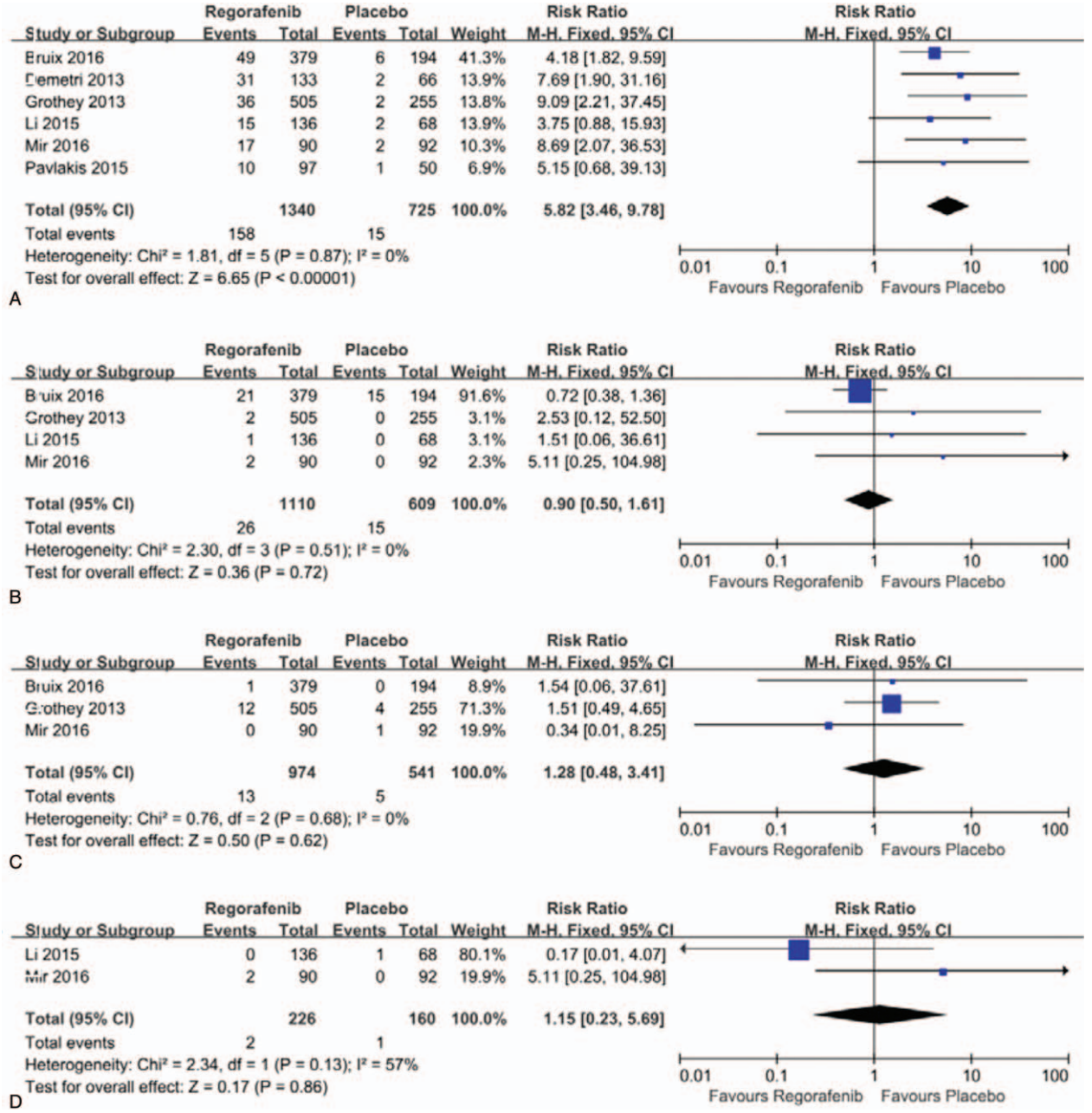

Figure 5. (A–D). Forest plots of relative risk of cardiovascular events of high-grade associated with regorafenib versus control. A. Hypertension; B. Hemorrhage; C. Thrombosis; D. Heart failure.

monitoring procedure, as well as precautionary measures established. However, cardiovascular toxicities of targeted drugs, the emerging effective and convenient ones in recent years, have also been reported in clinical researches, such as anti-Her-2 drugs,[12,20–22] anti-VEGFR drugs,[13,23] EGFR-TKIs,[24–26] and multi-target agents,[27,28] with mechanism of which still remains controversial.

Regorafenib, the multi-targeted agent, has also been reported considerable cardiovascular toxicities, and even fatal events.[4,6] According to the present pooled analysis, hypertension and hemorrhage seem to be the most significant cardiovascular events, with their incidence rate at all-grade as 36.8% and 8.6%, respectively, which was accordance with the data from former researches on other multi-targeted drugs, such as pazopanib, vandetanib, and axitinib. The incidence rate of hypertension with those multi-targeted drugs ranges from 30% to 50% of dose-dependent, of which the elevation of systemic blood pressure (SBP) from 20 to 30 mmHg, and increasing of diastolic blood pressure (DBP) from 9 to 17 mmHg.[28] Likewise, hypertension induced or aggravated intracranial hemorrhage (ICH), should been cared in clinical application. Additionally, other than ICH, regorafenib-induced hemorrhage has also been shown as nosebleed,[3] gastrointestinal bleeding,[3] and esophagorrhagia,[6] which might should not attributed to the exacerbation of hypertension merely. Results from several researches have revealed that hypertension and bleeding caused by those agents was resulted from endothelial dysfunction, dysfunctional nitric oxide metabolism, and vascular rarefaction, which was parallel

to bevacizumab.[29] In addition, the destruction of pericytes, which are essential for blood vessel formation and maintenance, should also be considered responsible for agents-induced hypertension and hemorrhage. However, specific mechanism of hypertension or hemorrhage caused by regorafenib and multi-targeted drugs still remains doubtful.

Comparatively, relative risks of the other cardiovascular events induced by regorafenib, thrombosis, and heart failure, appear no statistical significance compared with placebo in present study, which seems better tolerated compared with other analogous agents. Sunitinib has been reported with a particularly high risk of congestive heart failure (CHF) (8.0%–12.5%), with a decrease in left ventricular ejection fraction (LVEF) of 1.5% to 2.0% after each cycle of treatment.[30,31] Besides, a former pooled analysis of randomized controlled trials involving 10,255 patients was conducted to evaluate the risk of arterial thrombotic events in patients treated with sorafenib or sunitinib, the results of which suggested that the RR of arterial thrombotic events related to sorafenib and sunitinib was 3.03 (95% CI: 1.25–7.37; $P = .015$) compared with the control,[32] result of which has been further identified by another meta-analysis regarding the cardiotoxicity of sorafenib and sunitinib.[33] Cabozantinib, another multi-targeted agent, targeting FLT3, KIT, MET, RET, and VEGFR2, was showed with severe pulmonary embolism at an incidence rate of 6% according to a phase II randomized discontinuation trial in patients with advanced prostate cancer.[34] Pazopanib, was even reported companied with pulmonary embolism at an incidence rate up to 10%, including 3% fatal events of that, in patients with advanced GIST.[35] However, as the diversity of carcinomas and characteristic of patients between regorafenib and other multi-targeted drugs, the superiority of thrombosis and heart failure with regoranib should be judged more prudent further.

As the apparent adverse events of hypertension of targeted agents, some solutions have been attempted for the prevention and treatment. Angiotensin-converting enzyme inhibitors (ACEI) and β-blockers have been shown to improve myocardial energetics, and further attenuate the degree of cell death, which results from sunitinib-induced apoptosis.[36] Additionally, thalidomide was also reported that it could protect pericyte survival, and reduce sunitinib-induced cardiovascular events without influencing its anticancer efficacy.[37] Metformin, the historic antidiabetic, was showed with preventing stress-induced left ventricular dysfunction as well according to vivo researches.[38] More studies on protective agents and deepgoing researches on mechanism of cardiovascular events of multi-targeted drugs including regorafenib have been conducted to provide alternative therapies.

It should be acknowledged that a number of limitations were existed in present meta-analysis, the most obvious one is the heterogeneity, which caused by the diversity of dose of regorafenib and tumor types in the included patients. We have tried to perform a meta-regression to solve the problem. However, we cannot specify the relevant coefficient, especially among studies of single-armed model (24/30), which comes to be one of the limitations of our study. Furthermore, the value of the present pooled analysis was limited by the respective limitations of included researches, which comes to be the common deficiency of meta-analysis. Finally, RR of heart failure was based on merely 2 placebo-controlled trials due to the missing data of other literatures, which should has brought controversial outcome of that. Thus, we could not establish more convinced results with the limitations.

In conclusion, the present meta-analysis has demonstrated that regorafenib is associated with an increasing risk of hypertension at all-grade and high-grade, as well as hemorrhage at all-grade compared with control. Adequate awareness of cardiovascular adverse events of regorafenib should be established for clinicians.

Author contributions

Data curation: Jianxin Chen.
Investigation: Junhui Wang.
Methodology: Jianxin Chen.
Project administration: Jianxin Chen.
Software: Jianxin Chen, Junhui wang.
Supervision: Jianxin Chen, Junhui Wang.
Visualization: Jianxin Chen.
Writing – original draft: Jianxin Chen.
Writing – review & editing: Jianxin Chen.

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