# Incidence and Risk of Sorafenib-Induced Hypertension: A Systematic Review and Meta-Analysis

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Hypertension is one of the major side effects of sorafenib, and reported incidences vary substantially among clinical trials. A systematic review was conducted using Medline, PubMed, Embase, and the Cochrane Library for all longitudinal studies to investigate the incidence and risk of hypertension events in cancer patients treated with sorafenib. A total of 14 randomized controlled trials and 39 prospective single-arm trials involving 13,555 patients were selected for the meta-analysis. The relative risk of all-grade and high-grade hypertension associated with sorafenib were 3.07 (95% confidence interval [CI], 2.05–4.60; $P<.01$) and 3.31 (95% CI, 2.21–4.95; $P<.01$), respectively. The overall incidence of sorafenib-induced all-grade and high-grade hypertension were 19.1% (95% CI, 15.8%–22.4%) and 4.3% (95% CI, 3.0%–5.5%), respectively. A significantly higher incidence of hypertension was noted in patients with renal cell carcinoma (RCC) compared with those with non-RCC malignancies (all-grade: 24.9% [95% CI, 19.7%–30.1%] vs 15.7% [95% CI, 12.1%–19.3%]; $P<.05$; high-grade:8.6% [95% CI, 6.0%–11.2%] vs 1.8% [95% CI, 0.9%–2.6%]; $P<.05$). The trials with median progression-free survival (PFS) longer than 5.3 months (mean PFS) demonstrated a significantly higher incidence of high-grade hypertension than trials with shorter PFS (6.3% [95% CI, 4.1%–8.5%] vs 2.6% [95% CI, 1.4%–3.8%]; $P<.05$). Findings of the meta-analysis indicated a significantly high risk of sorafenib-induced hypertension. Patients with RCC have a significantly higher incidence of hypertension and the occurrence of hypertension may be associated with improved prognosis. *J Clin Hypertens (Greenwich).* 2014;16:177–185. ©2014 Wiley Periodicals, Inc.

Targeted agents have substantially improved the outcome of patients with cancer. Sorafenib, as the first multikinase inhibitor and one of the most widely used small-molecule oral-targeted drugs, has a broad spectrum of antitumor activity that induces both tumor apoptosis and disruption of the tumor vasculature.[1] At present, sorafenib is recommended as the standard first-line treatment for advanced hepatocellular carcinoma (HCC),[2] the second-line treatment for advanced renal cell carcinoma (RCC),[3] and, more recently, the treatment of late-stage (metastatic) differentiated thyroid cancer (http://www.fda.gov). New indications and treatment modalities of sorafenib are being explored by current clinical research for a wide range of tumors, for instance, prostate cancer and melanoma.[4–6]

Hypertension is one of the common side effects associated with sorafenib and has been noted in clinical trials with high incidence. In clinical trials, the onset of hypertension in sorafenib-treated patients can occur at any time during therapy and the reported incidences of hypertension associated with sorafenib therapy vary substantially. Although a previous meta-analysis[7] reported a significant increase in the risk of hypertension with sorafenib, these estimates are based on only a small number of studies of varying quality, and, as much of the evidence relates to patients with RCC, they may not be applicable for patients with other types of malignancies. Moreover, the risk factors for the development of hypertension, an important issue in reducing the risk of occurrence, have not been elucidated. In the past 5 years, many more prospective clinical trials with larger sample size and various types of malignancies have been performed. We proposed that pooling the analyses of recent studies could provide a better understanding on the overall risk of hypertension and the underlying risk factors. Therefore, we performed a systematic review and meta-analysis of the published prospective studies to further investigate the incidence and risk of hypertension associated with sorafenib.

## MATERIALS AND METHODS

### Data Sources

We systematically searched the electronic databases Medline, PubMed, EMBASE, Society of Clinical Oncology annual meetings (http://www.asco.org), and the Cochrane Library for Central Register of Clinical Trials, using the MESH terms "sorafenib," with the key words "cancer" and "clinical trial." We limited our search to studies in human patients and English language in peer-reviewed journals from 1966 to October 2013. The reference lists of identified articles and bibliographies of original articles were also reviewed. The articles that were not freely available to us were requested from the authors.

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**Manuscript received:** October 24, 2013; **revised:** November 30, 2013; **accepted:** December 8, 2013
**DOI: 10.1111/jch.12273**

### Study Selection

Trials that met the following criteria were chosen for analysis: (1) randomized controlled trials (RCTs) that directly compared cancer patients treated with and without sorafenib; prospective uncontrolled single-arm trials in which sorafenib as a single systematic administration was given at a starting dose of 400 mg twice a day; (2) safety data available for the events or incidences of hypertension; and (3) at least 20 patients were enrolled in every clinical trial. Data extraction was conducted independently by two investigators (LY and LS) and according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (www.prisma-statement.org). Any discrepancies were resolved by consensus. We mainly extracted the following information: first author's name; year of publication; trial design; number of enrolled patients; treatment arms; number of cases in the treatment and placebo groups (when available); underlying malignant disease; median age; median treatment duration; median progression-free survival (PFS); adverse outcomes of hypertension; and doses and schedules used.

### Clinical Endpoints

Clinical endpoints were selected from the safety profile of each trial. Hypertension was recorded according to versions 2 or 3 of the Common Terminology Criteria for Adverse Events (CTCAE; http://ctep.cancer.gov): grade 1, asymptomatic, transient (<24 hours) increase in blood pressure (BP) by >20 mm Hg (diastolic) or to >150/100 mm Hg if previously within normal limits, intervention not indicated; grade 2, recurrent or persistent (>24 hours) or symptomatic increase by >20 mm Hg (diastolic) or to >150/100 mm Hg if previously within normal limits, monotherapy might be indicated; grade 3, >1 drug needed for treatment or more intensive treatment than used previously; and grade 4, life-threatening consequences (eg, hypertensive crisis). We included the incidence of hypertension of grade I or above in our analysis. We included the incidence of all-grade and high-grade hypertension (grade 3 or above) in our analysis.

### Statistical Analysis

Stata statistical software package (release 11.2; Stata Corporation, College Station, TX) was used for statistical analysis. The proportion of both all-grade and high-grade (grade 3 and 4) hypertension were derived from each study. For studies with a control group, the relative risk (RR) of hypertension was also calculated. For the meta-analysis, we used a fixed-effects (weighted with inverse variance) or random-effects model.[8] The Cochran's $Q$ statistic and $I^2$ statistics were first calculated to assess the heterogeneity among the proportions of the included trials. If the $P$ value was <.1, the assumption of homogeneity was deemed invalid, and the random-effects model was reported after exploring the causes of heterogeneity.[9] Otherwise, the fixed-effects model was reported. Subgroup analyses were performed to identify risk factors with sorafenib-based therapy. Publication bias was quantified by Begg's test and Egger's test. A 2-tailed $P$ value <.05 was considered statistically significant. We also used funnel plots to evaluate the publication bias.

## RESULTS

### Patient Characteristics

Our search yielded 264 clinical studies, of which 211 were initially excluded. After evaluating each remaining study, a total of 53 studies with 13,555 patients were available for analysis (Figure 1). The main characteristics of the included trials are presented in Table I. The baseline Eastern Cooperative Oncology Group performance status for most patients was between 0 and 1. Malignant diseases included were RCC (12 studies), HCC (7 studies), prostate cancer (5 studies), thyroid cancer (3 studies), sarcomas (3 studies), melanoma (4 studies), non–small-cell lung cancer (6 studies), breast cancer (2 studies), gallbladder carcinoma and cholangiocarcinoma (1 study), squamous cell carcinoma of the head and neck (1 study), neuroendocrine tumor (1 study), gastric stromal tumor (1 study), squamous cell carcinoma of the head and neck/nasopharyngeal carcinoma (1 study), uterine carcinoma/carcinosarcoma (1 study), osteosarcoma (1 study), mesothelioma (1 study), lymphoma (1 study), and acute myelocytic leukemia (1 study). The starting dose and schedule of

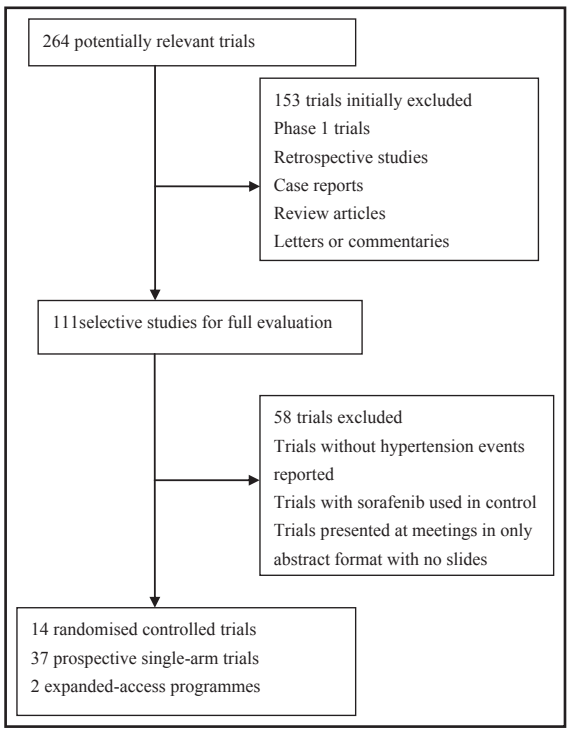


**FIGURE 1.** Selection process for trials.

**TABLE I.** Characteristics of Clinical Trials and Patients Included in the Meta-Analysis

| Trial | Trial Design | Patients Enrolled, No. | Sample Size, No. | Treatment Arms | Median Age, y | Underlying Malignancy | Median TD, mo | Median PFS, mo |
|---|---|---|---|---|---|---|---|---|
| Ratain[30] | Single-arm phase II | 202 | 202 | Sorafenib 400 mg BID | 58 | RCC[a] | 3 | 6 |
| Escudier[31] | Randomized phase III | 903 | 451 | Sorafenib 400 mg BID/ placebo | 58 | RCC | 5.7 | 5.5 |
| Stadler[32] | EAP | 2502 | 2502 | Sorafenib 400 mg BID | 63 | RCC | 5.5 | 9 |
| Escudier[33] | Randomized phase II | 189 | 97 | Sorafenib 400 mg bid/ placebo | 62 | RCC | 6 | 5.7 |
| Procopio[34] | Single-arm phase II | 128 | 62 | Sorafenib 400 mg BID | 62 | RCC | 6.8 | 7 |
| Rini[35] | Randomized phase III | 723 | 362 | Sorafenib 400 mg BID/ axitinib | 61 | RCC | 5 | 4.7 |
| Di Lorenzo[36] | Single-arm phase II | 52 | 52 | Sorafenib 400 mg BID | 60 | RCC | 4.3 | 4 |
| Akaza[37] | Single-arm phase II | 131 | 131 | Sorafenib 400 mg BID | 63 | RCC | 7 | 7.5 |
| Beck[38] | EAP | 1159 | 1145 | Sorafenib 400 mg BID | 62 | RCC | NR | 6.6 |
| Zhang[39] | Single-arm phase II | 98 | 98 | Sorafenib 400 mg BID | NR | RCC | 19 | 15 |
| Garcia[40] | Single-arm phase II | 47 | 47 | Sorafenib 400 mg BID | 64 | RCC | 3 | 4.4 |
| Motzer[41] | Randomized phase III | 517 | 257 | Sorafenib 400 mg BID/ tivozanib | 50 | RCC | NR | 9.1 |
| Kudo[42] | Randomized phase III | 458 | 229 | Sorafenib 400 mg BID/ placebo | 69 | HCC[a] | 4 | 5.4[a] |
| Llovet[43] | Randomized phase III | 602 | 297 | Sorafenib 400 mg BID/ placebo | 65 | HCC | NR | 4.1 |
| Cheng[44] | Randomized phase III | 271 | 149 | Sorafenib 400 mg BID/ placebo | 51 | HCC | NR | 2.8[a] |
| Sansonno[45] | Randomized phase II | 80 | 40 | Sorafenib 400 mg BID/ placebo | 73 | HCC | NR | 9.2[a] |
| Yau[46] | Single-arm phase II | 51 | 51 | Sorafenib 400 mg BID | 56 | HCC | 3 | 3 |
| Di Costanzo[47] | Single-arm phase II | 116 | 116 | Sorafenib 400 mg BID | 67 | HCC | 3 | 12[a] |
| Duan[48] | Single-arm phase II | 52 | 52 | Sorafenib 400 mg BID | 51 | HCC | NR | 10 |
| Steinbild[49] | Single-arm phase II | 57 | 55 | Sorafenib 400 mg BID | 70 | Prostate cancer | 3 | 2 |
| Safarinejad[6] | Single-arm phase II | 64 | 64 | Sorafenib 400 mg BID | 69 | Prostate cancer | 1.5 | 2.9 |
| Aragon-Ching[50] | Single-arm phase II | 24 | 24 | Sorafenib 400 mg BID | 66 | Prostate cancer | NR | 3.7 |
| Dahut[51] | Single-arm phase II | 22 | 22 | Sorafenib 400 mg BID | 64 | Prostate cancer | 1 | 1.8 |
| Chi[52] | Single-arm phase II | 28 | 28 | Sorafenib 400 mg BID | 67 | Prostate cancer | 2 | 2.3 |
| Scagliotti[53] | Randomized phase II | 922 | 43 | CP+sorafenib 400 mg BID/CP+placebo | 62 | NSCLC[a] | 3.9 | 4.6 |
| Paz-Ares[54] | Randomized phase III | 769 | 385 | GC+sorafenib 400 mg BID/GC+placebo | 60 | NSCLC[a] | 4 | 6 |
| Dingemans[55] | Single-arm phase II | 59 | 59 | Sorafenib 400 mg BID | 58.5 | NSCLC[a] | 2.1 | 2.3 |
| Wakelee[56] | Single-arm phase II | 333 | 333 | Sorafenib 400 mg BID | 64 | NSCLC[a] | 2 | 2.3 |
| Blumenschein[57] | Single-arm phase II | 54 | 52 | Sorafenib 400 mg BID | NR | NSCLC[a] | 2.3 | 2.7 |
| Spigel[58] | Randomized phase II | 165 | 111 | Erlotinib+sorafenib 400 mg BID/erlotinib+placebo | 65 | NSCLC | NR | 3.9 |
| Eisen[59] | Single-arm phase II | 502 | 37 | Sorafenib 400 mg BID | 53 | Melanoma | 3 | 2.6 |
| Ott[5] | Single-arm phase II | 36 | 36 | Sorafenib 400 mg BID | 64 | Melanoma | 2 | NR |
| McDermott[29] | Randomized phase II | 101 | 51 | DTIC+sorafenib 400 mg BID/DTIC+placebo | 58 | Melanoma | 4.5 | 4.9 |
| Flaherty[60] | Randomized phase III | 790 | 393 | CP+sorafenib 400 mg BID/CP+placebo | 16 | Melanoma | 5 | 4.9 |
| Gupta-Abramson[4] | Single-arm phase II | 30 | 30 | Sorafenib 400 mg BID | 63 | Thyroid cancer | 6.3 | 18.4 |
| Kloos[61] | Single-arm phase II | 56 | 56 | Sorafenib 400 mg BID | 61 | Thyroid cancer | 10.4 | 15 |
| Savvides[62] | Single-arm phase II | 20 | 20 | Sorafenib 400 mg BID | 59 | Thyroid cancer | 2 | 1.9 |
| Moreno-Aspitia[63] | Single-arm phase II | 23 | 23 | Sorafenib 400 mg BID | 54 | Breast cancer | 2 | 2 |
| Baselga[64] | Randomized phase II | 224 | 112 | Capecitabine+sorafenib 400 mg BID/ capecitabine+placebo | 55 | Breast cancer | 7.7 | 6.4 |
| Elser[65] | Single-arm phase II | 27 | 26 | Sorafenib 400 mg BID | 53 | SCCHN/NPC | 2 | 1.8[a] |
| Williamson[66] | Single-arm phase II | 41 | 41 | Sorafenib 400 mg BID | 63.5 | SCCHN[a] | NR | 4 |

**TABLE I.** Characteristics of Clinical Trials and Patients Included in the Meta-Analysis (Continued)

| Trial | Trial Design | Patients Enrolled, No. | Sample Size, No. | Treatment Arms | Median Age, y | Underlying Malignancy | Median TD, mo | Median PFS, mo |
|---|---|---|---|---|---|---|---|---|
| Maki[67] | Single-arm phase II | 145 | 144 | Sorafenib 400 mg BID | 55 | Sarcomas | 3 | 3.2 |
| Grignani[68] | Single-arm phase II | 35 | 35 | Sorafenib 400 mg BID | 21 | Osteosarcoma | 4.4 | 4 |
| von Mehren[69] | Single-arm phase II | 51 | 37 | Sorafenib 400 mg BID | 63 | Sarcomas | NR | 3 |
| Santoro[70] | Single-arm phase II | 100 | 100 | Sorafenib 400 mg BID | 54 | Sarcomas | 1 | 4.2 |
| Hobday[71] | Single-arm phase II | 93 | 93 | Sorafenib 400 mg bid | 59 | NET | NR | NR |
| Nimeiri[72] | Single-arm phase II | 56 | 56 | Sorafenib 400 mg BID | 64 | UC/CS | 3 | 3.2 |
| El-Khoueiry[73] | Single-arm phase II | 36 | 31 | Sorafenib 400 mg BID | 57 | GC/CC | 2 | 3 |
| Dubey[74] | Single-arm phase II | 51 | 50 | Sorafenib 400 mg BID | 69 | Mesothelioma | 3 | 3.6 |
| Park[75] | Single-arm phase II | 31 | 31 | Sorafenib 400 mg BID | 59 | GST[a] | 5.7 | 4.9 |
| Guidetti[76] | Single-arm phase II | 30 | 30 | Sorafenib 400 mg BID | 61 | Lymphoma | 4 | 4 |
| Serve[77] | Randomized phase II | 197 | 102 | SC+sorafenib 400 mg BID/SC+placebo | NR | AML | NR | 7 |
| Goncalves[78] | Randomized phase III | 102 | 50 | Gemcitabine+sorafenib 400 mg BID/ gemcitabine+placebo | 61 | Pancreatic cancer | 2 | 3.8 |

Abbreviations: A, Asian population; AML, acute myelocytic leukemia; BID, twice daily; C, Caucasian; CP, carboplatin and paclitaxel chemotherapy; EAP, expanded access program; GC, gemcitabine and cisplatin chemotherapy; GC/CC, gallbladder carcinoma and cholangiocarcinoma; GST, gastric stromal tumor; HCC, hepatocellular carcinoma; M, multiple race; NET, neuroendocrine tumor; NR, not reported; NSCLC, non–small-cell lung carcinoma; PFS, progression-free survival; RCC, renal cell cancer; SCCHN, squamous cell carcinoma of the head and neck; SCCHN/NPC, squamous cell carcinoma of the head and neck/nasopharyngeal carcinoma; TD, treatment duration; UC/CS, uterine carcinoma/carcinosarcoma; SC, standard 7 + 3 induction chemotherapy plus two cycles of consolidation therapy with intermediate dose (6×1 g/sqm) AraC. Only Time to Progression was reported.

sorafenib was based on that currently approved by the US Food and Drug Administration (400 mg, orally, twice daily) in each trial.

## RR of Hypertension Events

We calculated the RR of all-grade and high-grade hypertension associated with sorafenib treatment compared with the control treatment from 14 randomized controlled trials (2930 patients in the sorafenib group and 2790 patients in the control group). Using a random-effects model, the RR of all-grade hypertension associated with sorafenib vs control was 3.07 (95% confidence interval [CI], 2.05–4.60; $P<.01$; Figure 2). The RR of high-grade hypertension associated with sorafenib vs control was 3.31 (95% CI, 2.21–4.95; $P<.01$) as calculated using the fixed-effects model (Figure 3). Stratified analysis by the presence or not of concomitant chemotherapy demonstrated similar risks (Table II).

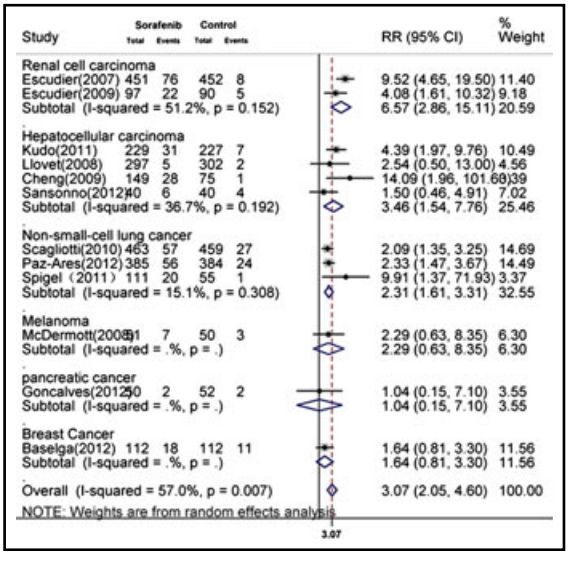


**FIGURE 2.** Meta-analysis of the relative risk (RR) of developing all-grade hypertension in cancer patients receiving sorafenib. CI indicates confidence interval.

## Incidence of Hypertension Events

In the incidence analysis, 7109 patients were included for all-grade hypertension events, and 7853 were included for high-grade events. This numerical difference was attributable to the fact that some trials reported only all-grade events and others high-grade events alone. Using a random-effects model, we determined that the overall incidence of all-grade hypertension in patients receiving sorafenib was 19.1% (95% CI, 15.8%–22.4%). The overall incidence of high-grade hypertension was 4.3% (95% CI, 3.0%–5.5%; Figure 4).

In the subgroup analysis, we first determined whether patients with RCC were associated with a higher risk for hypertension relative to other cancer patients. As shown in Table III, a significant difference of the incidence of all-grade hypertension was noted between patients with RCC and those with non-RCC malignancies (24.9% [95% CI, 19.7%–30.1%] vs 15.7% [95% CI, 12.1%–19.3%], $P<.05$). The incidence of sorafenib-associated

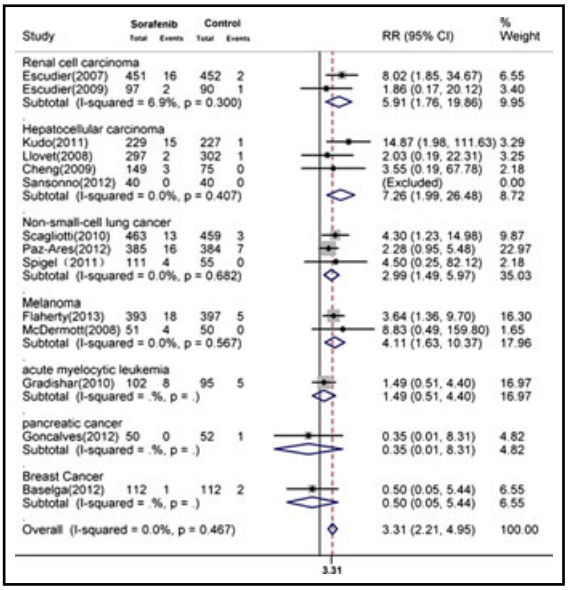


**FIGURE 3.** Meta-analysis of the relative risk (RR) of developing high-grade hypertension in cancer patients receiving sorafenib. CI indicates confidence interval.

high-grade hypertension was also significantly higher for patients with RCC (8.6% [95% CI, 6.0%–11.2%]) than those with non-RCC (1.8% [95% CI, 0.9%–2.6%]).

To further understand whether the treatment duration and PFS were related to the risk of sorafenib-induced hypertension, we stratified the trials according to the median treatment duration time (4.1 months) and median PFS (5.3 months) of included trials. The trials with median PFS longer than 5.3 months demonstrated a significantly higher incidence of high-grade hypertension compared with trials with shorter PFS (6.3% [95% CI, 4.1%–8.5%] vs 2.6% [95% CI, 1.4%–3.8%], $P<.05$). No differences were recorded in the subgroup analysis based on treatment duration (Table III). We did not perform a subgroup analysis based on race because most trials enrolled patients of multiple races.

### Publication Bias

No evidence of publication bias was detected for the incidence or RR of hypertension of this study by either the Begg's or the Egger's test ($P>.1$). The shapes of the funnel plots did not reveal any evidence of obvious asymmetry visually (Figure 5).

## DISCUSSION

In the present meta-analysis, we not only showed a relatively more accurate incidence of hypertension associated with sorafenib, but also provided a better understanding of risk factors for sorafenib-induced hypertension. In contrast to the previous study,[7] our study showed a potentially higher incidence of both all-grade and high-grade hypertension in patients with RCC than those with other malignances. One possible explanation for this is the unique biology of RCC. Individuals with RCC usually have an inactivation of the von-Hippel Lindau gene, which impairs the degradation of hypoxia-inducible factor and, in turn, could increase vascular endothelial growth factor (VEGF).[10] Therefore, blockade of the VEGF pathway in patients with RCC who have pre-existing unregulated VEGF in the endothelial cell microenvironment may substantially impair endothelial function. In addition, patients with RCC can be more susceptible to developing hypertension because of previous nephrectomy and renal dysfunction.

One of the most remarkable outcomes of our meta-analysis is that the incidence of sorafenib-induced high-grade hypertension was significantly higher in trials with a median PFS >5.3 months compared with those with a

**TABLE II.** Relative Risk of Sorafenib-Associated Hypertension vs Control From Randomized Controlled Trials of Cancer Patients Stratified by Underlying Malignancy and Concomitant Chemotherapy

| | | Sample Size | | | Relative Risk of Hypertension | | |
|---|---|---|---|---|---|---|---|
| Subgroup | Study, No. | Sorafenib | Control | All-Grade | 95% CI | High-Grade | 95% CI |
| Stratified by underlying malignancy | | | | | | | |
| RCC | 2 | 548 | 542 | 6.57 | 2.86–15.11 | 5.9 | 1.76–19.86 |
| HCC | 4 | 715 | 644 | 3.46 | 1.54–7.76 | 7.26 | 1.99–26.48 |
| NSCLC | 2/1 | 959 | 898 | 2.31 | 1.62–3.31 | 2.99 | 1.49–5.97 |
| Melanoma | 3 | 494 | 447 | 2.29 | 0.63–8.35 | 4.12 | 1.63–10.37 |
| Pancreatic cancer | 1 | 50 | 52 | 1.04 | 0.15–7.10 | 0.35 | 0.01–8.31 |
| Breast cancer | 1 | 112 | 112 | 1.64 | 0.81–3.31 | 0.5 | 0.05–5.44 |
| AML | 1 | 102 | 95 | – | – | 1.49 | 0.51–4.40 |
| Stratified by concomitant chemotherapy | | | | | | | |
| Without | 6 | 1263 | 1186 | 4.59 | 2.50–8.40 | 6.54 | 2.70–15.84 |
| With | 8 | 1667 | 1604 | 2.14 | 1.62–2.82 | 2.57 | 1.62–4.07 |

Abbreviations: AML, acute myelocytic leukemia; CI, confidence interval; HCC, hepatocellular carcinoma; NSCLC, non–small-cell lung carcinoma; RCC, renal cell carcinoma.

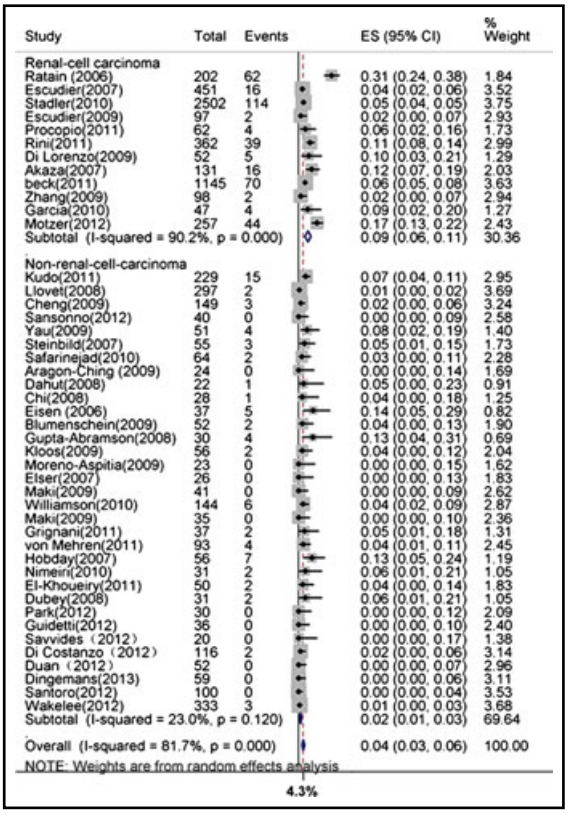


**FIGURE 4.** Meta-analysis of incidence of high-grade hypertension in cancer patients receiving sorafenib. ES indicates effect size; CI, confidence interval.

median PFS <5.3 months. Several studies have shown that early BP rise was associated with better anti-tumor efficacy and improved prognosis.[11–13] A retrospective analysis focusing on sunitinib, another angiogenesis inhibitor, demonstrated that systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg were associated with significantly better outcomes compared with those with lower systolic BP and diastolic BP (median overall survival of 30.5 months vs 7.8 months and 32.1 months vs 15 months, respectively).[14] A more recent study evaluating the effect of sorafenib on patients with HCC showed that patients who had documented hypertension had significantly better overall survival (18.2 months vs 4.5 months; $P$=.016).[11] The present study supported the hypothesis that the development of hypertension was correlated with improved outcomes.

Multiple mechanisms could be involved in the pathogenesis of sorafenib-associated hypertension. The postulated mechanism includes abnormalities of nitric oxide (NO) pathway, endothelial dysfunction, and capillary rarefaction. The VEGF signaling pathway, as the primary target of multikinase inhibitor, is known to augment the transcription of endothelial NO synthase, leading to the increased production of NO.[15] The inhibition of VEGF signaling pathway by sorafenib is, therefore, considered one of the major contributors to the development of hypertension, through vasoconstriction as a result of decreased NO. Furthermore, NO plays a direct role in controlling the vascular tone of glomerular arterioles, pressure natriuresis, and tubuloglomerular feedback.[16] Therefore, reduction of NO synthesis can result in sodium retention, which may increase the severity of hypertension. Another postulated mechanism of hypertension induced by sorafenib therapy is called "rarefaction," which means a reduction in capillary density. Since VEGF has been demonstrated to provide a survival signal to maintenance of endothelial viability,[17] inhibition of the VEGF signaling pathway can induce endothelial cell apoptosis, reduction in capillary density and microvascular flow, and thus increase the afterload.[18,19] Platelet-derived growth factor (PDGF), another target of sorafenib, functions mainly to enhance vascular smooth muscle cells or pericytes recruitment for maturation and stabilization of new vessels. Inhibition of PDGF/PDGF receptor may result in an inability to stabilize new vessels in the myocardium, which also contributes to the occurrence of hypertension.[20] In addition, sorafenib may directly

**TABLE III.** Incidence of Sorafenib-Associated Hypertension in Cancer Patients Stratified by Underlying Malignancy, Median Treatment Duration, and PFS

| Subgroup | Study, No. All-Grade/High-Grade | Sample Size All-Grade/High-Grade | Incidence of Hypertension All-Grade, % | 95% CI | High-Grade, % | 95% CI |
|---|---|---|---|---|---|---|
| Stratified by underlying malignancy | | | | | | |
| Renal | 12/11 | 5406/5149 | 24.90 | 19.7–30.1 | 8.60 | 6.0–11.2 |
| Other | 28/34 | 2452/2704 | 15.7 | 12.1–19.3 | 1.80 | 0.9–2.6 |
| Stratified by treatment duration | | | | | | |
| >4.1 months | 13/13 | 4204/4205 | 21.50 | 15.7–27.3 | 4.60 | 2.7–6.5 |
| <4.1 months | 21/23 | 1779/1910 | 18.30 | 13.1–23.6 | 4.90 | 2.6–7.3 |
| Stratified by PFS | | | | | | |
| >5.3 months | 16/15 | 5515/5468 | 22.50 | 18.0–26.9 | 6.30 | 4.1–8.5 |
| <5.3 months | 23/29 | 2050/2329 | 16.90 | 12.5–21.4 | 2.60 | 1.4–3.8 |

Abbreviations: CI, confidence interval; PFS, progression-free survival.

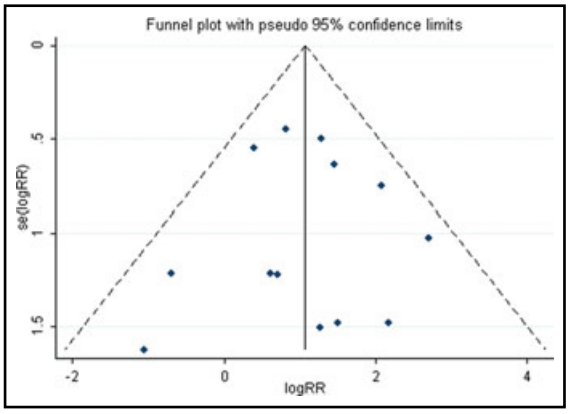


**FIGURE 5.** Funnel plot of the meta-analysis (relative risk [RR] for high-grade hypertension).

impact angiotensin II–mediated BP control by interfering with angiotensin II–dependent activation of tyrosine kinase receptors.[21] Finally, none of the multikinase inhibitors are truly specific, and occurrence of hypertension may be correlated with lack of target specificity.

Potentially devastating consequences such as arterial thromboembolic events may be related to the hypertension.[22,23] Therefore, the prevention and treatment of hypertension are critically important. Since patients with RCC have a significantly higher incidence of hypertension, more attention should be paid to the occurrence of hypertension in these patients. According to the National Cancer Institute Investigational Drug Steering Committee,[24] patients should be advised to seek treatment to control preexisting hypertension before the start of sorafenib therapy. BP should be monitored weekly during the first cycle of angiogenesis inhibitor therapy and then at least every 2 to 3 weeks for the duration of treatment. Patients who develop stage 1 hypertension (>140/90 mm Hg) or an increase in diastolic BP ≥20 mm Hg from baseline should initiate antihypertensive therapy. The goal for hypertension control in patients receiving angiogenesis inhibitors therapy is a maximum BP of 140/90 mm Hg, and efforts to reach this goal should begin before initiation of therapy. While there is still no clear recommendation regarding the pharmacologic management of sorafenib-induced hypertension, several preclinical and retrospective studies may give us some direction. An animal experiment demonstrated that treatment with captopril not only attenuated sorafenib-induced hypertension but also decreased glomerular injury.[25] A retrospective review found that bevacizumab-induced hypertension could be controlled by a single antihypertensive drug, but higher starting doses were required (eg, median dose, 20 mg of quinapril).[26] More recently, another retrospective study showed that amlodipine 5 mg daily controlled BP in a majority of patients with mild toxicity.[27] In addition, the nondihydropyridine calcium channel blockers verapamil and diltiazem are CYP3A4 inhibitors and nifedipine has been shown to induce VEGF secretion.[28] Hence, these drugs are not recommended for the treatment of angiogenesis inhibitor–induced hypertension.

## STUDY LIMITATIONS

Our study has the following limitations. First, the prevalence of baseline hypertension and information on pretreatment of hypertension was not described in the included trials, which may have led to an inaccurate estimation of the incidence of sorafenib-associated hypertension. Second, there was heterogeneity in a number of relevant aspects (such as patient clinical profiles and length of follow-up) among clinical trials, and the incidences of hypertension showed significant heterogeneity among the included studies. Third, the studies included in this meta-analysis were conducted at various institutions by different investigators with patients of different nationalities/ethnicities, and these differences may have biased the reported incidences. Fourth, there was no standardization of the methods for measuring BP, and the definition or grading of hypertension varied between studies, which are potentially confounding factors. Finally, although we concluded that higher BP may predict a longer PFS, various confounding factors cannot be assessed properly and incorporated into the analysis.

## CONCLUSIONS

Despite the limitations of our meta-analysis, we conclude that the widely used agent sorafenib is associated with a high risk of hypertension in patients with cancer. This study will enable physicians to more accurately advise patients on the risk of hypertension associated with sorafenib therapy. For patients with RCC receiving sorafenib, physicians should be highly vigilant in the prevention and treatment of high-grade hypertension. Further studies are recommended to investigate the RR and proper management of sorafenib-induced hypertension.

*Acknowledgments and disclosures: Yan Li and Shun Li contributed equally to this study. We declare that we have no conflict of interest.*

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