Risk of Dyslipidemia Associated with VEGF/VEGFR Inhibitors: A Meta-Analysis

Huihui Dai a,1, Chang Liu a,1, Peijuan Li a, Zhangfeng Mai a, Xiaoming Tan a, Sijing Chen a, Ziling Zhou a, Zhiben Tang a, Jingwei Miao a, Lihong Liu b,⁎, Yi Fang a,⁎

a Phase I Clinical Research Unit, The Sixth Affiliated Hospital of Guangzhou Medical University, Qingyuan People’s Hospital, No. B24, Yinquan road, Qingyuan district, Qingyuan city, Guangdong Province, China 511518
b Department of Pharmacy, Peking University People’s Hospital, Beijing, China. 100034

OBJECTIVE: This meta-analysis was performed to investigate hyperlipidemia in patients with carcinoma treated with vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR) inhibitors.

METHODS: We searched for eligible phase II and III studies using PubMed and Embase databases. We then summarized reported occurrences of hyperlipidemia in patients with different cancers. Relative risk ratios (RRs) and 95% confidence intervals (CIs) were calculated by Revman 5 software in meta-analysis. RESULTS: Eleven trials (4760 subjects) were included in this meta-analysis. Overall, VEGF/VEGFR inhibitors had similar incidence of hypertriglyceridemia (RR = 0.56, 95% CI = 0.24%-1.32%, P = .19), hypercholesterolemia (RR = 1.15, 95% CI = 0.42%-3.16%, P = .78), and LDL elevation (RR = 4.58, 95% CI = 0.80%-26.25%, P = .09) than control drugs, under high heterogeneity. Moreover, subgroup analyses found VEGF/VEGFR inhibitors had higher incidence of hyperglyceridemia (RR = 1.86, 95% CI = 1.37%-2.52%, P < .001) and hypercholesterolemia (RR = 2.95, 95% CI = 2.02%-4.30%, P = .006) than blank control or placebo control drugs (placebo-controlled-group), although with lower incidence of hyperglyceridemia (RR = 0.29, 95% CI = 0.12%-0.69%, P < .001) and hypercholesterolemia (RR = 0.39, 95% CI = 0.20%-0.56%, P < .001) than placebo controls (positive-controlled-groups).

CONCLUSION: The use of VEGF/VEGFR inhibitors, especially the multitargeted VEGF tyrosine kinase inhibitors (VEGFR-TKIs), was associated with higher risk of hyperlipidemia than the use of placebo, but this risk was less than that associated with mTOR or FGFR inhibitors. It indicated that clinicians need to pay close attention to the occurrence of hyperlipidemia in VEGFR-TKIs therapies.

© 2020 The Sixth Affiliated Hospital of Guangzhou Medical University, Qingyuan People’s Hospital. Published by Elsevier Inc on behalf of Neoplasia Press, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Vascular endothelial growth factor (VEGF) plays an important role in tumor growth, invasion, and metastasis by promoting angiogenesis. Small-molecule VEGF-tyrosine kinase inhibitors (TKIs) and VEGF-binding antibodies are used against various solid tumors and have been shown to improve overall survival in patients with cancer [1]. These targeted drugs also show a better safety profile than that of traditional chemotherapeutics.

Advanced tumors rely on receiving sufficient blood supply, and tumors in the vicinity of vasculature and grow along these vessels. This phenomenon, called vessel co-option, is particularly important for metastasis and often occurs in highly vascularized connective tissues [2].

The process of neovascularization requires multiple steps involving various cells including vascular endothelial cells, macrophages, and fibroblasts, as well as interaction between signaling proteins such as VEGF, fibroblast growth factor (FGF), and hypoxia-inducible factor-I (HIF-1) [3]. Among these, the most critical factor is VEGF because it stimulates endothelial cells to secrete proteases and plasminogen activators, leading to the degradation of the vessel basement membrane [4].

VEGF family includes VEGF A/B/C/D and placental growth factor [3]. Receptors of the VEGF family, VEGFR-1/2/3, are receptor tyrosine kinases. VEGF-Rs are mainly distributed in endothelial cells, bone marrow–derived cells, and neuronal cell membranes.

ARTICLE INFO

Article history:
Received 17 October 2019
Accepted 2 April 2020
Available online xxxx

ABSTRACT

OBJECTIVE: This meta-analysis was performed to investigate hyperlipidemia in patients with carcinoma treated with vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR) inhibitors.

METHODS: We searched for eligible phase II and III studies using PubMed and Embase databases. We then summarized reported occurrences of hyperlipidemia in patients with different cancers. Relative risk ratios (RRs) and 95% confidence intervals (CIs) were calculated by Revman 5 software in meta-analysis. RESULTS: Eleven trials (4760 subjects) were included in this meta-analysis. Overall, VEGF/VEGFR inhibitors had similar incidence of hypertriglyceridemia (RR = 0.56, 95% CI = 0.24%-1.32%, P = .19), hypercholesterolemia (RR = 1.15, 95% CI = 0.42%-3.16%, P = .78), and LDL elevation (RR = 4.58, 95% CI = 0.80%-26.25%, P = .09) than control drugs, under high heterogeneity. Moreover, subgroup analyses found VEGF/VEGFR inhibitors had higher incidence of hyperglyceridemia (RR = 1.86, 95% CI = 1.37%-2.52%, P < .001) and hypercholesterolemia (RR = 2.95, 95% CI = 2.02%-4.30%, P = .006) than blank control or placebo control drugs (placebo-controlled-group), although with lower incidence of hyperglyceridemia (RR = 0.29, 95% CI = 0.12%-0.69%, P < .001) and hypercholesterolemia (RR = 0.39, 95% CI = 0.20%-0.56%, P < .001) than placebo controls (positive-controlled-groups).

CONCLUSION: The use of VEGF/VEGFR inhibitors, especially the multitargeted VEGF tyrosine kinase inhibitors (VEGFR-TKIs), was associated with higher risk of hyperlipidemia than the use of placebo, but this risk was less than that associated with mTOR or FGFR inhibitors. It indicated that clinicians need to pay close attention to the occurrence of hyperlipidemia in VEGFR-TKIs therapies.

© 2020 The Sixth Affiliated Hospital of Guangzhou Medical University, Qingyuan People’s Hospital. Published by Elsevier Inc on behalf of Neoplasia Press, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
The VEGF-TKIs inhibit vascular germination and block the downstream signaling pathway, thereby destroying the tumor angiogenesis network [3]. Bevacizumab is an anti-human VEGF-A recombinant monoclonal antibody. In vitro and in vivo preclinical studies indicate that bevacizumab inhibits endothelial cell proliferation, vascular permeability, and angiogenesis [5].

Presently, VEGFR-TKIs and anti-VEGF antibody are widely used as first- and second-line drugs against various advanced cancers. The US Food and Drug Administration has approved eight VEGF-TKIs, sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, lenvatinib, and bevacizumab, against various cancers. VEGFR-TKIs are also widely used against advanced cancers. Clinical application of VEGFR-TKIs has been expanding because anticancer drugs are now covered by medical insurance in China. This highlights the need to evaluate differences in the toxicity profiles of traditional cytotoxic and targeted drugs. However, few reports have discussed dyslipidemia occurring postapplication of targeted drugs.

In this study, we performed a meta-analysis examining randomized controlled trials (RCTs) of VEGFR-TKIs and anti-VEGF antibody drugs. This was done to systematically evaluate the effect of VEGF/VEGFR inhibitors on blood lipid levels. In this study, we discuss the mechanisms driving the activity of these drugs and assess treatment prognoses. By doing so, we hope to provide clinicians with important information for deciding the strategy of medication.

Material and Methods

Search Strategy

We searched for RCTs published in English before March 2019 and available in PubMed and Embase databases; the search was conducted according to the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. By combining keywords with free words, we searched for the keywords of the drug names combined with “Random and Controlled”. In addition, we did a manual search to supplement the results based on the review articles retrieved related to the drugs and their citations. Additionally, we used the website http://www.ClinicalTrials.gov to obtain supplementary information and published research results corresponding to the RCTs found in this study.

Data Inclusion and Exclusion Criteria

Included study type: RCTs published in English; no limitation on minimum number of enrolled subjects;
Subject: adult (age > 18 years old) patients with cancer;
Intervention drugs: VEGFR-TKIs and anti-VEGF monoclonal antibodies approved for clinical first-line and/or second-line therapy by US Food
and Drug Administration, EMA, or National Medical Products Administration (NMPA). The following drugs were included: a flibercept, anlotinib, axitinib, cabozantinib, dovitinib, erlotinib, gefitinib, pazopanib, pegatinib, sorafenib, sunitinib, pandetanib, patalanib, famitinib, lenvatinib, bevacizumab, and ramucirumab.

Outcome indicators and determination criteria: hyperlipidemia (including hypercholesterolemia, hypertriglyceridemia, or mixed hyperlipidemia). Severity of adverse events (AEs) was classified based on the Common Terminology Criteria for Adverse Events published by the US National Institutes of Health.

Exclusion criteria: non-RCT studies, such as reviews and guidelines, literature containing published abstracts only, nonclinical research reports employing subjects such as animals and cells, noncomparative joint treatment reports, and literature for which full text or data were unavailable.

### Table 1

**Characteristics of Included Studies**

| Author          | Year | Phase | Subject | Racial | DT              | DC              | AEs | N_{AEs} of DT | N_{AEs} of DC | mPFS (Months) | Total ≥ G3 | Total ≥ G3 |
|-----------------|------|-------|---------|--------|-----------------|-----------------|-----|--------------|--------------|---------------|------------|------------|
| Armstrong [14]  | 2016 | II    | mNSCLC  | Multiple | Sunitinib | Everolimus   | T: 8.3 | HT            | 0            | 5             | G3:3       |            |
| Brown [13]      | 2016 | c     | reGBM   | British | Cediranib + gefitinib | Cediranib + placebo | T: 3.6 | HT            | 0            | 1             | 1          |            |
| Choueiri [16]   | 2015 | III   | a/mRCC  | Multiple | Cabozantinib | Everolimus   | T: 7.4 | C: 2.8       | 0            | 1             | 1          | 1          |
| Flaherty [15]   | 2015 | II    | mRCC   | Multiple | Sorafenib + temsirolimus | Bevacizumab + temsirolimus | T: 7.4 | C: 3.8       | 5            | 1             | 0          | 0          |
| Han [11]        | 2018 | II    | raNSCLC| Chinese | Anlotinib | Placebo   | T: 4.8 | C: 9.2        | 5            | 0             | 0          | 0          |
| Han, B. [12]    | 2018 | III   | aNSCLC | Chinese | Anlotinib | Placebo   | T: 4.8 | C: 9.2        | 5            | 0             | 0          | 0          |
| Hutson [10]     | 2014 | III   | mRCC   | Multiple | Sorafenib | Tensirolimus | T: 3.9 | C: 4.3       | 18           | 1             | 53         | 8          |
| Kerr [9]        | 2016 | III   | CRC    | Multiple | Capecitabine + bevacizumab | Capecitabine | T: 24-48 w | C: 24 w | 2            | 1            | 0          | 0          |
| McKay [8]       | 2016 | II    | CRPC   | Multiple | ADT + bevacizumab | ADT Alone | T: 13.3 | C: 13.2 | 1           | 0            | 0          | 0          |
| Motzer [7]      | 2014 | III   | mRCC   | Multiple | Borafenib | Dovitinib | T: 3.6 | C: 3.7       | 2           | 1             | 55         | G3: 27     |
| Rui-Hua Xu [6]  | 2017 | II    | mCRC   | Chinese | Farnitinib | Placebo   | T: 2.8 | P: 1.5       | 11           | 0             | 0          | 0          |

\(D_T\), test drugs; \(D_C\), control drugs; G, grade indicating the severity of AEs that depends on the Common Terminology Criteria for Adverse Events; mPFS, median progression-free survival; mNSCLC, metastatic non–clear cell renal cell carcinomas; reGBM, recurrent glioblastoma; a/mRCC, advanced or metastatic renal cell carcinoma; raNSCLC, refractory advanced non–small cell lung cancer; CRC, metastatic colorectal adenocarcinoma; CRPC, castration-resistant prostate cancer; ADT, androgen deprivation therapy; HC, hypercholesterolemia; HT, hypertriglyceridemia; ELDL, low-density lipoprotein elevation; w, weeks. □ 743 (76% of 968) patients in the capecitabine + bevacizumab group and 746 (77% of 973) in the capecitabine-alone group received 24 weeks of capecitabine; 699 (72%) patients received more than 24 weeks of bevacizumab, with 536 (55%) receiving 48 weeks.

Replaced by RFS (median relapse-free survival), 10.2 months for ADT alone and 13.3 months for ADT + bevacizumab.

**Extraction and Quality Evaluation of Data**

The literature was evaluated by two researchers independently. When their opinion whether to include a study differs, they discussed and then made a decision with a third researcher. Selection, performance, detection, attrition, and reporting bias, as well as other biases with respect to included literature, were assessed using RCT quality assessment criteria listed in the Cochrane Handbook for Systematic Reviews (Version 5). A data extraction table was designed to independently extract data related to results specified previously. Missing, dubious, or divergent data were included only after discussion.

The information extracted included author, publication year, basic characteristics of the included subjects, sample size of the test and control groups, intervention strategy and dose, treatment and follow-up time, and outcomes for the following AEs: hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, and increased LDL.

![Figure 2. Bar diagram of bias risk.](image-url)
Statistical Analyses

Statistical analysis and graphing of the data were performed using Review Manager 5.3. Occurrence of AEs was a binomial variable represented by the risk ratio (RR) value and corresponding 95% confidence interval (CI). Heterogeneity was assessed using the $P$ value of $Q$ test and $I^2$ measure. Heterogeneity between studies was considered small if $P > .10$. $I^2 < 25\%$ indicated no heterogeneity, $25\% \leq I^2 < 50\%$ indicated low heterogeneity, $50\% \leq I^2 < 75\%$ indicated moderate heterogeneity, and $I^2 \geq 75\%$ indicated high heterogeneity between studies. A subgroup analysis was then used to analyze factors possibly leading to heterogeneity. Sensitivity analyses were performed, and a funnel plot was used for publication-bias analysis. If more than 10 documents were included, results would be compared with the combined results.

Results

Search Results

The literature search initially retrieved 3618 articles. After removing repetitive results, 1046 articles remained; 163 articles were retained based on article title and abstract, and then 37 eligible studies involving phase II and III trials were selected. Among these, 11 studies [6–16] met the inclusion criteria (Figure 1); these studies reported dyslipidemia events related to VEGF/VEGFR inhibitors, which involved the following drugs: anlotinib, axitinib, cabozantinib, gefitinib, dovitinib, sorafenib, sunitinib, famitinib, and bevacizumab.

Characteristics of the Included Studies

Six of 11 studies [6,8,11,13–15] were phase II, and the other 5 studies [7,9,10,12,16] were phase III, which included 2495 and 2265 subjects, respectively. Patients were from China, Japan, Germany, America, Asia, Africa, or Europe with different cancers. The following test drugs were involved: sunitinib, gefitinib, anlotinib, cabozaantinib, sorafenib, famitinib, and bevacizumab. Characteristics of the included studies are shown in Table 1.

Methodological Quality and Bias Assessment

The methodological quality of all included studies was assessed using the Cochrane Collaboration risk of bias tool (Figures 2 and 3). None of all randomized trials was stopped early or has attrition or reporting bias. Nine [7,9–16] and 4 [6,11–13] trials reported adequate allocation concealment and double blinding. All articles were reported specific registry numbers except one [8].

Meta-Analysis Results of Dyslipidemia

Hypertriglyceridemia

Ten studies [6–10,12–16] reported on the occurrence of hypertriglyceridemia. The experimental groups showed a lower incidence rate of hypertriglyceridemia compared with that of control groups. Heterogeneity between the studies with respect to the incidence rate of hypertriglyceridemia showed statistically significant differences ($P <$ 0.05).
The results of meta-analysis, obtained via random effects model, showed that the incidence rate of hypertriglyceridemia in the experimental group was nonsignificantly lower ($P = .19$) than that in the control group during the observation period (RR = 0.56, 95% CI = 0.24%-1.32%) (Figure 4).

We performed a subgroup analysis based on the type of control used in the studies.

Among the five studies using placebo as control, three [6,12,13] compared VEGFR-TKIs versus placebo, and two [8,9] compared bevacizumab joint therapy versus blank. Meta-analysis result showed that the incidence rate of hypertriglyceridemia was higher in the experimental subgroup than the placebo-controlled subgroup (RR = 1.86, 95% CI = 1.37%-2.52%). There was no statistically significant difference in heterogeneity between five studies ($P = .68$, $I^2 = 0%$).

The test drugs of all the experimental groups were VEGFR-TKIs in the other five positive controlled studies; one [15] of them combined sorafenib with mTOR inhibitor temsirolimus. The incidence rate of hypertriglyceridemia was lower in the experimental subgroup than in the positive-controlled subgroup (RR = 0.29, 95% CI = 0.12%-0.69%); the heterogeneity between the five studies was statistically different ($P = .001$, $I^2 = 78%$), as shown in Figure 5.

Among the eight studies reporting hypercholesterolemia, seven [6,10–15] used VEGFR-TKIs to treat the experimental group, and one [9] used bevacizumab combined with capecitabine. The incidence rate of hypercholesterolemia did not show statistically significant differences between experimental and control groups. Meta-analysis conducted using a random effects model (heterogeneity: $P < .001$, $I^2 = 87$%) showed that incidence rate of hypercholesterolemia in the experimental group was similar ($P = .78$) to that in the control group (RR = 1.15, 95% CI = 0.42%-3.16%) (Figure 6).

Subgroup analysis was performed based on the type of control used in the studies and using the random effects model.

Among the five studies using placebo as control, three [6,11,12] compared VEGFR-TKIs against placebo, and one [9] compared combined treatment with bevacizumab and capecitabine against that using capecitabine only, and one of them [13] compared gefitinib combined with cediranib against cediranib alone. Among the three positive-controlled studies, two studies [10,14] were on VEGFR-TKIs versus an mTOR inhibitor, and one study [15] compared sorafenib with sirolimus combined therapy against that using bevacizumab combined with sirolimus. There was no significant difference in heterogeneity between studies in the two subgroups ($P = .58$, $I^2 = 0%$; $P = .39$, $I^2 = 0%$).
The results showed that the incidence rate of hypercholesterolemia in the experimental subgroup was higher than in the placebo-controlled subgroup (RR = 2.95, 95% CI = 2.02%-4.30%) and lower than in the positive-controlled subgroup (RR = 1.06, 95% CI = 0.41%-2.74%), as shown in Figure 7.

**LDL Elevation**

Two [11,12] of all 11 studies, which compared anlotinib against placebo, reported AEs involving LDL elevation with almost moderate heterogeneity (P = .17, I² = 48%). Meta-analysis (random effects model) result showed that incidence rate of LDL elevation in the experimental group was higher than that in the control group (RR = 4.58, 95% CI = 0.80%-26.25%) (Figure 8).

**Publication Bias**

In the analyses of hypertriglyceridemia (10 studies) and hypercholesterolemia (8 studies), at 95% CI, four funnel plots fell outside the dotted line, respectively. Thus, these indicated the presence of publication bias in this study, as shown in Figure 9.

**Discussion**

In patients with tumors, common grade 3 or 4 AEs to VEGF/VEGFR inhibitors include hypertension, fatigue, hand-foot syndrome, elevated lipase levels, lymphopenia, and neutropenia [9,17,18]. In healthy individuals, early phase clinical trials of VEGF/VEGFR inhibitors showed no specific adverse reactions [19,20]. A number of studies have shown that VEGF/VEGFR inhibitors can induce thrombosis [21]. Dyslipidemia may promote or intensify the formation of blood clots. When blood lipids are too high, they can form deposits on blood vessel walls, inducing or aggravating atherosclerosis, which might lead to stroke, renal arteriosclerosis, and limb necrosis.

A retrospective study of 155 clinical trials of VEGFR-TKIs in patients with mRCC showed that hypothyroidism or hyperlipidemia may be an effective predictor of response to VEGFR-TKIs in patients with mRCC. Another trial [22] also showed that VEGFR-TKIs can cause AEs involving dyslipidemia. This notion remains to be confirmed, but it is important to monitor blood lipid levels during administration of VEGFR-TKIs. We believe that the risk of dyslipidemia related to use of VEGF/VEGFR inhibitors, especially VEGFR-TKIs, should be addressed to some extent. However, heretofore, the mechanisms involved in dyslipidemia caused by VEGF/VEGFR inhibitors remain unclear.

Yet, there were few studies that reported on dyslipidemia associated with the use of VEGF/VEGFR inhibitors and that systematically explored the relationship or incidence between them. For that reason, we performed a preliminary meta-analysis to compare the incidence rate of dyslipidemia in the experimental and control groups of eligible phase II and III studies evaluating VEGF/VEGFR inhibitors. Considering the focus on the effects of VEGFR-TKIs, our study compared sorafenib and bevacizumab under conditions of joint treatment with sirolimus also included.

As shown by our meta-analysis, overall comparison of the incidence rates of hypertriglyceridemia and hypercholesterolemia showed high heterogeneity, whereas, except for the subgroup which compared with the positive-controlled-group of hypertriglyceridemia, I² of other subgroup analyses, which were based on treatment administered (placebo or positive control) to the control drugs, was 0% (Figures 4 and 6). It indicated that the results of subgroups were robust.
These results demonstrated that the groups treated with VEGF/VEGFR inhibitors showed higher incidence rate of AEs involving hypertriglyceridemia, hypercholesterolemia, and elevated LDL compared with that of the placebo-controlled-groups. However, compared with positive-controlled-groups, the incidence rate of hypertriglyceridemia and hypercholesterolemia was lower in the groups treated with VEGF/VEGFR inhibitors.

The positive-controlled-groups included in our study were treated with everolimus [14,16] and temsirolimus [10] which were mTOR inhibitors, bevacizumab [15].

The incidence rate of hypertriglyceridemia for only one study [15] using bevacizumab as positive control showed an RR of 1.04 (Figure 4). Yet in the other studies, the incidence rate of hypertriglyceridemia and hypercholesterolemia with positive control (mTOR inhibitors and dovitinib) was higher than the experimental group (Figures 4 and 5).

According to existing reports, mTOR inhibitors, also used against tumors such as RCC, are associated with more metabolic-related grade 3 and 4 AEs, such as hypertriglyceridemia, elevated glucose, and hypophosphatemia [23]. Recent studies have shown that the use of mTOR inhibitors can lead to elevated levels of blood sugar and lipids [24,25]. Because VEGF binds to VEGFR to activate the AKT/mTOR pathway [26,27], blocking the VEGF pathway also indirectly inhibits the mTOR pathway, which may be associated with a relative increase in blood lipid levels. So we predict the elevated levels of blood lipids resulting from the use of VEGF/VEGFR inhibitors may be associated with indirect inhibition of the mTOR pathway.

Furthermore, increased blood lipid levels caused by multitarget VEGFR-TKIs may also stem from the inhibitory effect of FGFR. In addition to controlling cellular proliferation, differentiation, and survival, endocrine GFG also regulates the metabolism of phosphate, bile acids, carbohydrates, and lipids [28]. Specific activation of FGFR participates in the regulation of metabolism [29].

Although as a multitarget TKI dovitinib also can inhibit VEGFR, it mainly acts on FGFR1/3, FLT3, and c-Kit. In the study by Motzer et al. [8], hypertriglyceridemia only occurred in 2/284 (0.704%) patients in the sorafenib-treated group, and only one of them developed grade 3 AEs. However, hypertriglyceridemia occurred in 55/280 (19.64%) individuals in the dovitinib-treated group, and 27 and 11 cases of grade 3 and 4 AEs were observed, respectively. In a phase II study [30] comparing a VEGF inhibitor and dovitinib for the treatment of patients with RCC, the incidence rate of AEs involving hypertriglyceridemia in the dovitinib-treated group was 7%.

In a phase II study [32] on therapy against mRCC, treatment with anlotinib, which mainly acts on VEGFR1/2/3, FGFR2, PDGFR, and c-Kit, resulted in higher incidence rate of hyperlipidemia than that with sunitinib (25.6% vs 11.6%). In the two studies [11,12] included in our analysis, the rate of hyperlipidemia-related AEs associated with the use of anlotinib was significantly higher than that of the placebo control group (Table 2).

In examining similar studies [33] during our review of the literature, we found that different VEGF/VEGFR inhibitors are associated with different rates and degrees of various AEs. This is likely related to differences in target-binding ability of TKIs and indications. The relationships between VEGF and atherosclerosis, hypertension, diabetes, and inflammation are complex.

Serum VEGF in patients with hyperlipidemia is significantly higher than that in normal people, while elevated VEGFR-R2 is associated with decreased VEGF concentrations in obese individuals [34]. As well, treatment with gefitinib decreases serum levels of total cholesterol, high-density lipoprotein, and low-density lipoprotein in mice fed a high-fat diet model [35], which indicates that reducing VEGF levels may mitigate the elevation of blood lipids. Moreover, bevacizumab and other monoclonal antibodies against VEGF do not affect increased levels of lipids in the blood, and such AEs are rarely reported. This indicates that the regulatory effect of VEGF/VEGFR inhibitors on blood lipids may be bidirectional, depending on the type of drug, target of action, tumor type, host factors, and concomitant anticancer drugs. This hypothesis, however, should be examined in animal models and clinical trials involving patients and healthy individuals.

In our study, the quality of included studies was high, although the number was few; subgroup analyses of AEs were performed, and the incidence of severe AEs was considered in the discussion.

This meta-analysis also had some limitations. The examined literature reported only the number and proportion of AEs involving dyslipidemia; none of them reported or included determined indicator values. Studies were conducted by different research groups in different international institutes, so potential bias, which may have been present in reporting the types of AEs, could not be avoided. Additionally, LDL elevation was only reported in

Table 2

| Study          | Phase | Anlotinib | Placebo |
|----------------|-------|-----------|---------|
|                |       | Total No. | ≥ G3     | Total No. | ≥ G3     |
| Han [11] II    | HCS   | 15 (25.00%)| 0       | 3 (5.26%) | 0       |
|                | LDL   | 10 (16.67%)| 0       | 0         | 0       |
| Han, B. [12] III | HTG  | 131 (44.6%) | 9 (3.1%) | 34 (23.8%)| 0       |
|                | HCS   | 123 (41.8%)| 0       | 20 (14.0%)| 0       |
|                | LDL   | 62 (21.1%) | 2 (0.7%) | 11 (7.7%) | 0       |

HCS, hypercholesterolemia; HTG, hypertriglyceridemia; LDL, low-density lipoprotein elevation.
two trials, from one pipeline of anlotinib, by Han, B et al. Therefore, the combination results only figured a trend and were not stable.

In summary, this study indicates that use of VEGFR/VEGFR inhibitors (especially VEGF-TKIs) could cause an increased risk of dyslipidemia, so the occurrence and the potential effects of them need to be paid more attention to. Moreover, this risk was primarily influenced by tumor type, host factors, and concomitant use of anticancer drugs. The results obtained in our analysis would help clinicians choose appropriate VEGFR/VEGFR inhibitors for the treatment of patients with cancer.

Acknowledgements

We'd like to show our gratitude to Mrs. Yang Liu (who had studied under professor Fang Yi) for sharing her pearls of wisdom with us during the course of this research, helping us to revise and sharing her comments on our earlier version of the manuscript. We also thank Dr. Teng Hua Wang (from The Fifth Affiliated Hospital of Guangzhou Medical University) for providing insights and expertise that greatly assisted the research. Any errors are our own and should not tarnish the reputations of these esteemed persons.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of Interest

The authors report no conflicts of interest in this work.

References

[1] W.X. Qi, D.L. Min, Z. Shen, Y.-J. Sun, F. Lin, L.-N. Tang, A.-N. He, Y. Yao, Risk of venous thromboembolic events associated with VEGFR-TKIs: a systematic review and meta-analysis, Int. J. Cancer 132 (2013) 2967–2974.

[2] T. Donnem, J. Hu, M. Ferguson, G. Adighibe, C. Snell, A.L. Harris, K.C. Gatter, F. Pezzella, Vessel co-option in primary human tumors and metastases: an obstacle to effective anti-angiogenic treatment? Cancer medicine 2 (2013) 427–436.

[3] M.J. Cross, FGF and VEGF function in angiogenic signalling pathways, biological responses and therapeutic inhibition, Trends Pharmacol. Sci. 22 (2001) 201–207.

[4] Y. Lai, Z. Zhao, T. Xing, Z. Liang, D. Chen, X. Duan, G. Zeng, W. Wu, Crousttalk between VEGFR and other receptor tyrosine kinases for TKI therapy of metastatic renal cell carcinoma, Cancer Cell Int. 18 (2018) 31.

[5] L.G. Presta, H. Chen, S.J. O’Connor, V. Chisholm, Y.G. Meng, L. Krummen, M. Winkler, Fang Yi, do the AKT/mTOR/p70S6K1 signalling pathway in human epithelial ovarian cancer, Cancer Cell Int. 18 (2018) 31.

[6] A.P. Zhou, J. Ma, Y. Bai, Y. Song, H. Li, X. Xie, X.B. Ren, D. Ye, J.-W. Bi, L.-W. Ma, J. Lei, Q. Yang, H. Yu, Famitinib versus placebo in the treatment of refractory metastatic renal cell carcinoma: a single center study, Chin. Med. J. 126 (2013) 4277–4281.

[7] T.E. Hutton, R.A. Figlin, J.G. Kuhn, R.J. Motzer, Targeted therapies for metastatic renal cell carcinoma: an overview of toxicity and dosing strategies, Oncologist 13 (2008) 1084–1096.

[8] B. Bouillot, P. Buffle, S. Smart, P. Ambarchian, B. Cariau, V. Bégues, Expert opinion on the metabolic complications of mTOR inhibitors, Ann. Endocrinol. 79 (2018) S93–S99.

[9] R.J. Motzer, C. Therasse, C. Boross, S. Dancey, M. Feng, C. Freilinger, M. Cohn, Management of side-effects of targeted therapies in renal cell cancer: endpoint side-effects and metabolic disorders, Bull Cancer 99 (2012) S47–S59.

[10] R.A. Figlin, A. Maity, PISK/mTOR pathway in angiogenesis, Front. Mol. Neurosci. 9 (2016) 51.

[11] B.X. Trinh, W.A.A. Tjasma, P.B. Vermeulen, G. Van den Eynden, I. Van der Auwerda, S.J. Van Laere, J. Hellemans, E.M.J.M. Berns, L.Y. Dirix, P.A. van Dam, The VEGF pathway and the AKT/mTOR/p70S6K1 signalling pathway in human epithelial ovarian cancer, Br. J. Cancer 100 (2009) 971.

[12] D.M. Ornitz, N.J.W.I.R.-D.B. Inth, The fibroblast growth factor signaling pathway 4 (2015) 215–266.

[13] V.J.M. Nien, G. Sancar, W. Liu, T. Van Zutphen, D. Struik, R.T. Yu, A.P. Atkins, R.M. Evans, J.W. Jonker, M.F.E.I. Downes, Fibroblast growth factor signaling in metabolic regulation 6 (2016) 193.

[14] V. Grünwald, M. Retz, M. Gravis, G. Manseau, Malignant epithelial diseases, Vascular toxicity and thromboembolism in solid cancer, Cardiovasc. Interv. Ther. 21 (2013) 493–499.

[15] K.T. Flaherty, J.B. Manola, M. Pinz, D.F. McDermott, M.B. Atkins, J.J. Dutcher, D.J. George, Euracelum versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPN): A multicentre, open-label, randomised phase 2 trial, The Lancet Oncology 17 (2016) 378–388.

[16] K.T. Flaherty, J.B. Manola, M. Pinz, D.F. McDermott, M.B. Atkins, J.J. Dutcher, D.J. George, K.A. Margolin, R.S. DiPaolo, BEST: A randomized phase II study of vascular endothelial growth factor, Raf kinase, and mammalian target of rapamycin combination targeted therapy with bevacizumab, sunitinib, and temsirolimus in advanced renal cell carcinoma—a trial of the ECOG-ACRIN cancer research group (E2804), J. Clin. Oncol. 33 (2015) 2384–2391.

[17] T.K. Choueiri, B. Esteban, T. Powles, P.N. Mainwaring, B.I. Rini, F. Donkova, H. Hammers, T.E. Hutton, J.L. Lee, K. Petelina, B.J. Roth, G.A. Bjarnason, L. Gecci, B. Keam, P. Maroto, D.Y.C. Heng, M. Schmidinger, P.W. Kantoff, A. Bogrmang-Hague, C. Hessel, C. Scheffeld, G.M. Schwab, N.M. Tannir, R.J. Motzer, Cabozantinib versus everolimus in advanced renal-cell carcinoma, N. Engl. J. Med. 373 (2015) 1814–1823.

[18] J.R. Bexst, P. Ranjan, R. Qin, H. Pittet, J. Pircs, G. Liu, T. Fitz, W.J. Maple, P.J.J. Flynn, B.F. Fruth, C. Erlichman, Safety and activity of temsirolimus and bevacizumab in patients with advanced renal cell carcinoma previously treated with tyrosine kinase inhibitors: a phase 2 consortium study, Cancer Chemother. Pharmacol. 75 (2015) 485–493.

[19] H. Miyake, S. Inki, K. Harada, M. Fujisawa, Absence of significant correlations of adverse events between first- and second-line tyrosine kinase inhibitors in patients with metastatic renal cell carcinoma, Critical genitourinary cancer 14 (2016) e19–e24.

[20] Y. Chen, J. Jiang, Z. Zhang, M.A. Tortorici, Y.K. Pitthavala, L. Gu, N.P. Hu, A Phase I study to evaluate the pharmacokinetics of axitinib (AG-3376) in healthy Chinese volunteers, Int. J. Clin. Pharmacol. Ther. 49 (2011) 679–687.

[21] Z. Hong, Q. Li, X. Zhu, W. Min, C. Li, X. Li, C. Liu, Z. Shen, Y. Ding, S. Hu, Association of variability and pharmacogenomics with bioequivalence of gefitinib in healthy male subjects, Front. Pharm. 9 (2018) 649.

[22] S. Kaadasent, A. Huseyn, C. Ishmael, Bevacizumab, bleeding, thromosis, and warfarin, Journal of Clinical Oncology Official Journal of the American Society of Clinical Oncology 21 (2003) 354–3543.

[23] W. Zhang, A.P. Zhou, Q. Qin, C.X. Chang, H.Y. Jiang, J.H. Ma, J.W. Wang, Famitinib in metastatic renal cell carcinoma: clinical efficacy of anlotinib on overall survival of patients with advanced non–small cell lung cancer, JAMA Oncology 4 (2018) 1569–1575.

[24] N. Brown, C. McBain, S. Nash, K. Hopkins, P. Sanghera, F. Saran, M. Phillips, F. Dungey, L. Clifton-Hadley, K. Wanek, D. Krell, S. Jeffries, I. Khan, P. Smith, P. Mulholland, Multi-center randomized phase II study comparing cediranib plus gefitinib with cediranib plus placebo in subjects with recurrent/progressive giloblastoma, PLoS ONE 11, 2016.

[25] A.J. Armstrong, S. Habali, T. Eisen, S. Broderick, W.M. Stadler, R.J. Jones, J.A. Garcia, U.N. Vaishampayan, J. Picus, R.E. Hawkinson, J.D. Hainsworth, C.K. Kollmannsberger, T.F. Logan, P. Puranov, A.C. Priest, C.W. Ryan, P. Beocerar, C.M. Lum, S. Oberg, D.J. George, Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPN): A multicentre, open-label, randomised phase 2 trial, The Lancet Oncology 17 (2016) 378–388.