Systematic Review of the Risk of Adverse Outcomes Associated with Vascular Endothelial Growth Factor Inhibitors for the Treatment of Cancer

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Abstract

Background: Anti-angiogenic therapy targeted at vascular endothelial growth factor (VEGF) is now used to treat several types of cancer. We did a systematic review of randomized controlled trials (RCTs) to summarize the adverse effects of vascular endothelial growth factor inhibitors (VEGFi), focusing on those with vascular pathogenesis.

Methods and Findings: We searched MEDLINE, EMBASE and Cochrane Library until April 19, 2012 to identify parallel RCTs comparing a VEGFi with a control among adults with any cancer. We pooled the risk of mortality, vascular events (myocardial infarction, stroke, heart failure, and thromboembolism), hypertension and new proteinuria using random-effects models and calculated unadjusted relative risk (RR). We also did meta-regression and assessed publication bias. We retrieved 83 comparisons from 72 studies (n = 38,078) on 11 different VEGFi from 7901 identified citations. The risk of mortality was significantly lower among VEGFi recipients than controls (pooled RR 0.96, 95% confidence interval [CI] 0.94 to 0.98, I² = 0%, tau² = 0; risk difference 2%). Compared to controls, VEGFi recipients had significantly higher risk of myocardial infarction (MI) (RR 3.54, 95% CI 1.61 to 7.80, I² = 0%, tau² = 0), arterial thrombotic events (RR 1.80, 95% CI 1.24 to 2.59, I² = 0%, tau² = 0); hypertension (RR 3.46, 95% CI 2.89 to 4.15, I² = 58%, tau² = 0.16), and new proteinuria (RR 2.51, 95% CI 1.60 to 3.94, I² = 87%, tau² = 0.65). The absolute risk difference was 0.8% for MI, 1% for arterial thrombotic events, 15% for hypertension and 12% for new proteinuria. Meta-regression did not suggest any statistically significant modifiers of the association between VEGFi treatment and any of the vascular events. Limitations include heterogeneity across the trials.

Conclusions: VEGFi increases the risk of MI, hypertension, arterial thromboembolism and proteinuria. The absolute magnitude of the excess risk appears clinically relevant, as the number needed to harm ranges from 7 to 125. These adverse events must be weighed against the lower mortality associated with VEGFi treatment.

Introduction

Angiogenesis is essential for tumour growth and blood borne metastasis [1], and vascular endothelial growth factor (VEGF) plays a key role in angiogenesis as well as the phenotyping of blood vessels in tumors [2]. Anti-angiogenic therapy targeted at VEGF inhibits vascular growth affecting the survival of certain tumor cells and has specificity through expression of specific markers by activated endothelium. Other mechanisms may also be important – such as improving blood perfusion, oxygenation or drug delivery [3–6]. Two major approaches for disrupting VEGF signaling include ligand blockade and pharmacologic inhibition. Ligand could be blocked through a monoclonal antibody (MoAb), soluble receptor/ligand trap, or an aptamer and signaling is inhibited by receptor targeting using a MoAb or a small-molecule tyrosine kinase (TK) inhibitor [7]. Several VEGF inhibitors (VEGF) have been approved by the Food and Drug Administration (FDA) for use in the treatment of cancer, beginning with bevacizumab for metastatic colorectal cancer in 2004 [1]. VEGFi are now used to treat multiple other types of cancer including lung adenocarcinoma, advanced renal cell carcinoma, gastrointestinal stromal tumor and medullary thyroid cancer. Although they have potentially important clinical benefits, VEGFi can also cause dose-dependent and dose-independent vascular adverse reactions [1,2,7,8]. FDA withdrew its approval of bevacizumab for breast cancer treatment in 2011, considering that the risk of such treatment would outweigh its benefits [9–12]. Given the mechanism of action for VEGFi, hypertension and ischemic coronary and cerebrovascular events have been of particular concern. Although arterial thrombosis, venous thrombosis, and compromise of vascular organs such as the kidney are also of potential concern, these adverse outcomes have...
been less well studied. We did this systematic review and meta-analysis to summarize available randomized trial evidence on the adverse effects of vascular endothelial growth factor inhibitors compared to control. Given the mechanism of action for VEGFi, we focused on adverse events that are related to vascular disease (myocardial infarction, stroke, heart failure, hypertension, thromboembolism, and proteinuria).

Methods

We did a systematic review and meta-analysis of published randomized clinical trials. We used accepted methods for literature searches, article selection, data extraction and risk of bias assessment and have reported our results according to published guidelines [13].

Data sources and searches

An expert librarian did a comprehensive search to identify all relevant studies regardless of language or publication status. MEDLINE (1950- April 19, 2012), EMBASE (1980- April 19, 2012) and Cochrane Library (April 19, 2012) were searched. The full search strategies are available in eTable S1. An academic subject-specialist and a statistician screened each citation or abstract. Trials considered to be relevant by any reviewer were retrieved for further review.

Intervention and comparison

VEGF inhibitor functions with a monoclonal IgG1 antibody against VEGF (such as bevacizumab); typical VEGF receptor inhibitor inhibits VEGF receptors on cancer cells (such as a tyrosine kinase inhibitor sunitinib) and atypical VEGF receptor inhibitor includes drugs having multikinase inhibitor properties such as sorafenib which inhibits VEGF receptors and the Raf cascade. A list of eligible VEGFi agents is shown in eTable S2. We compared VEGFi therapy to placebo (or no active intervention). Cointervention was allowed in both intervention and control arms.

Study selection

The full text of each potentially relevant study was independently assessed by two reviewers for inclusion in the review using predetermined eligibility criteria on a printed form. Parallel RCTs were eligible for inclusion if they involved adults (16 years or older) with cancer and included at least 30 participants in each treatment group; they compared a VEGFi with a control (placebo or no active treatment); and they reported one or more clinical outcomes (mortality, cardiovascular events [myocardial infarction, stroke, heart failure or hypertension], new proteinuria or thromboembolic events). The primary outcome measure was all-cause mortality. We excluded studies published in languages other than English; crossover studies were eligible but only results before the crossover were included. Disagreements were resolved by discussion and consultation with a third party. Disagreements arose with 4% of the articles (kappa = 0.90).

Data extraction and risk of bias assessment

We assessed and reported risks of bias in included studies using items from the Chalmers index (intention-to-treat, method of handling missing data) as well as items (concealment of allocation, randomization, blinding, loss-to-follow-up, funding sources, early stopping) that have been shown empirically to affect internal validity [14–18]. The following properties were extracted from each study: characteristics (country, VEGFi type and dose, duration of follow-up, duration of treatment, study cointervention(s), incident vs prevalent population [based on whether the index cancer had been previously treated or not], sample size), participants (age, gender, cancer type and stage, number of organs with metastases, prior chemotherapy or radiotherapy, Eastern Cooperative Oncology Group [ECOG] performance status), and results (number of events for subgroups, unadjusted and adjusted HR for eligible outcomes). The following outcomes were considered: all-cause mortality, cardiovascular events (myocardial infarction, stroke, heart failure, and hypertension), thrombosis (thrombotic/thromboembolic events, arterial thrombotic/thromboembolic events, venous thrombotic/thromboembolic events, and pulmonary embolism), and new proteinuria at the end of study. For each study, we used the definition of each outcome as provided by the authors of the source publication.

One reviewer extracted data from the selected trials. A second reviewer checked for accuracy. We preferentially captured intention-to-treat analyses where presented. Disagreements were resolved with the aid of a third party.

Data synthesis and analysis

We used Stata MP software (www.stata.com) to pool results using random-effects models. Dichotomous outcomes were summarized using the unadjusted relative risk (RR) and statistical heterogeneity was quantified using the I² statistic. We also used univariable meta-regression to examine whether certain variables (median age, percentage of male participants, VEGFi type, median duration of follow-up, median duration of treatment, incident population, cancer type, percentage of participants in cancer stages, number of organs with metastases, prior chemotherapy or radiotherapy, ECOG performance status), and study risks of bias influenced the association between VEGFi therapy and clinical outcome. We used random effect meta-regression. Log-RR was used as a summary statistics for the dependent variable. Publication bias was assessed by using weighted regression of data from trials that reported the frequency of the primary outcome by treatment group.

Results

Quality of research available

From 7901 identified citations, 458 articles were retrieved for detailed evaluation (Figure 1). Of these, 83 comparisons from 72 studies (n = 38,078) were eligible for inclusion in this review (Table 1 and eReference S1). Study sample sizes ranged from 61 to 2,670 (median 331); the median duration of treatment was 18 (range 3–90) weeks; the median duration of post-treatment follow-up was 15 (range 6–44) months. Details of the studies are summarized in eTable S3.

Risk of bias

The 72 studies had generally moderate to high risks of bias (see Figure 2 and eTable S4). The method of randomization was inappropriate or not reported in 68% of studies; 61% did not adequately conceal treatment allocation. Forty percent did not describe their study as double-blind (28% did not report that participants were blinded to their treatment). Only 38% fully reported losses to follow-up. Most (86%) were industry sponsored or partially industry sponsored trials. On the other hand, most trials exhibited certain markers of high quality (90% did not stop their study early and 85% used an intention-to-treat approach). We found no evidence of publication bias for all-cause mortality using a weighted regression test (bias = −0.34, p = 0.20; see eFigure S1).
Characteristics of trials and their participants

Of the eligible trials, 36 used a VEGF inhibitor (bevacizumab); 8 studies used a typical VEGF receptor inhibitor (axitinib in 3 trials, sunitinib in 3 trials, and cediranib in 2 trials); 29 trials used an atypical VEGF receptor inhibitor (vandetanib in 9 trials, sorafenib in 12 trials, vatalanib [hereafter referred to as its more commonly used name PTK/ZK] in 2 trials, pazopanib in 2 trials, neovastat in 2 trials, IM 862 in 1 trial, and motesanib in 1 trial, respectively). One trial had two active treatment arms (bevacizumab and motesanib) that were compared to placebo. Thirteen trials compared VEGFi therapy to placebo without any cointervention; the remainder included some type of chemotherapy cointerventions such as capecitabine, docetaxel or gemcitabine. The median age of study participants was 60 (range 48–71) years; the majority of patients were male (median 60%). Some studies reported cancer stage, ECOG performance status, previous chemotherapy or radiation therapy, and number of sites with metastases among study participants (see eTable S3).

Mortality

Thirty-seven trials (44 comparisons; n = 21,523) reported frequency of all-cause mortality at the end of study. Mortality was significantly lower among participants in the VEGFi treatment groups than in the control groups (RR 0.96, 95% confidence interval [CI] 0.94 to 0.98, $I^2 = 0\%$, tau2 = 0; see Figure 3); this corresponded to a risk difference of 2% (risk of death was 59% among participants in the control groups) and number needed to treat of 50.

Except for the presence of cointervention administered during the study (RR for trials with cointervention 0.97, 95% CI 0.95 to 0.99, $I^2 = 0\%$, tau2 = 0; RR for trials without cointervention 0.82, 95% CI 0.70 to 0.94, $I^2 = 19\%$, tau2 = 0.006, p = 0.007 for difference), none of the covariates considered (see methods)
Table 1. Brief description of included randomized trials.

| author       | year | Country                          | type of tumour/macular degeneration | VEGF\textsubscript{i} | cointervention | VEGF\textsubscript{i} weekly dose | sample size |
|--------------|------|----------------------------------|-------------------------------------|------------------------|----------------|-----------------------------------|-------------|
| Kabbinavar   | 2003 | USA                              | metastatic colorectal cancer        | bevacizumab            | FU/LV          | 2.5; 5 mg/kg                      | 104         |
| Yang         | 2003 | USA                              | metastatic RCC                      | bevacizumab            | none           | 1.5; 5 mg/kg                      | 116         |
| Hurwitz      | 2004 | USA, New Zealand, Australia      | metastatic colorectal cancer        | bevacizumab            | IFL            | 2.5 mg/kg                         | 813         |
| Johnson      | 2004 | USA                              | metastatic colorectal cancer        | bevacizumab            | carboplatin & paclitaxel | 2.5; 5 mg/kg | 99         |
| Kabbinavar   | 2005 | USA                              | metastatic colorectal cancer        | bevacizumab            | FU/LV          | 2.5 mg/kg                         | 209         |
| Miller       | 2005 | USA                              | metastatic breast cancer            | bevacizumab            | capcitabine    | 5 mg/kg                           | 462         |
| Demetri      | 2006 | USA, Canada, Australia, Italy, Singapore, UK, Belgium, France, Netherlands | gastrointestinal stromal tumour | sunitinib             | none           | 350 mg                            | 312         |
| Ratain       | 2006 | USA, UK                          | RCC                                 | sorafenib              | none           | 5600 mg                           | 65          |
| Sandler      | 2006 | USA                              | NSCLC                               | bevacizumab            | paclitaxel/carboplatin | 5 mg/kg | 850         |
| Arnold       | 2007 | Canada                           | SCLC                                | vandetanib             | none           | 2100 mg                           | 107         |
| Cohen        | 2007 | USA                              | NSCLC                               | bevacizumab            | carboplatin & paclitaxel | 5 mg/kg | 878         |
| Escudier*    | 2007 | France, USA, Poland, Canada      | metastatic RCC                      | Neovastat              | none           | 1680 ml                           | 300         |
| Escudier*    | 2007 | France, USA, UK, Poland, Germany | metastatic RCC                      | sorafenib              | none           | 5600 mg                           | 903         |
| Giantonio\textsuperscript{5} | 2007 | USA, South Africa                | metastatic colorectal cancer        | bevacizumab            | FOLFOX4        | 5 mg/kg                           | 432         |
| Herbst\textsuperscript{5}    | 2007 | USA                              | NSCLC                               | bevacizumab            | docetaxel/pemetrexed | 5 mg/kg | 61          |
| Heymach      | 2007 | USA, Czech Republic, Hungary     | NSCLC                               | vandetanib             | docetaxel      | 700; 2100 mg                      | 127         |
| Karrison     | 2007 | USA                              | malignant mesothelioma              | bevacizumab            | gemcitabine & cisplatin | 5 mg/kg | 108         |
| Mao          | 2007 | USA                              | prostate cancer                     | IM 862                 | none           | 70 mg                             | 71          |
| Miller       | 2007 | USA, Canada                      | metastatic breast cancer            | bevacizumab            | paclitaxel     | 5 mg/kg                           | 673         |
| Heymach\textsuperscript{6} | 2008 | USA, Spain, German, India, South Africa | NSCLC | vandetanib | paclitaxel & carboplatin | 2100 mg | 86          |
| Llovet       | 2008 | Europe, Australia, North America, South America | hepatocellular carcinoma | sorafenib             | none           | 5600 mg                           | 602         |
| McDermott    | 2008 | USA                              | melanoma                            | sorafenib              | dacarbazine    | 5600 mg                           | 101         |
| Saltz        | 2008 | USA, Canada, UK, Australia, Spain, Austria, Taiwan, Switzerland | metastatic colorectal cancer | bevacizumab            | XELOX or FOLFOX-4 | 2.5 mg/kg | 1400        |
| Spino        | 2008 | France, Spain, UK, Canada, USA, Italy | pancreatic cancer | axitinib | gemcitabine | 70 mg | 103          |
| Allegra      | 2009 | USA, Ireland                     | colon cancer                        | bevacizumab            | FOLFOX         | 2.5 mg/kg                         | 2670        |
| Cheng        | 2009 | Taiwan, China, South Korea       | hepatocellular carcinoma            | sorafenib              | none           | 5600 mg                           | 226         |
| Hauschchild  | 2009 | Germany, USA, France, Canada, Australia, UK, Netherlands | melanoma | sorafenib | carboplatin/paclitaxel | 5600 mg | 270         |

| author       | year | country                          | type of tumour/macular degeneration | VEGF\textsubscript{i} | cointervention | VEGF\textsubscript{i} weekly dose | sample size |
|--------------|------|----------------------------------|-------------------------------------|------------------------|----------------|-----------------------------------|-------------|
| Horti        | 2009 | Hungary, Germany, Brazil, Sweden, South Africa | metastatic prostate cancer         | vandetanib             | docetaxel & prednisolone | 700 mg | 86          |
| Van Cutsem   | 2009 | Belgium, France, Canada, Netherlands, Austria, Switzerland | metastatic pancreatic cancer      | bevacizumab            | gemcitabine & erlotinib | 2.5 mg/kg | 607         |
| Abou-Alfa    | 2010 | USA, UK, Canada, Russia, Argentina, China | hepatocellular carcinoma         | sorafenib              | doxorubicin    | 5600 mg                           | 96          |
| author         | year | Country                  | type of tumour/macular degeneration | VEGFi                  | cointervention                              | VEGFi weekly dose | sample size |
|----------------|------|--------------------------|------------------------------------|------------------------|---------------------------------------------|-------------------|-------------|
| Crown          | 2010 | Ireland, France, UK, Poland, USA | breast cancer                      | sunitinib              | capecitabine                               | 262.5 mg          | 442         |
| Escudier       | 2010 | Europe, Australia, Israel, Singapore, Taiwan | metastatic RCC                    | bevacizumab            | interferon alfa-2a                          | 5 mg/kg           | 649         |
| Goss           | 2010 | Canada, Brazil, Argentina, Romania, Australia, Singapore | NSCLC                             | cediranib              | carboplatin/paclitaxel                      | 210 mg            | 251         |
| Herbst         | 2010 | USA, China, Germany, Belgium, Japan, Netherlands | NSCLC                             | vandetanib             | docetaxel                                   | 700 mg            | 1391        |
| Kemeny         | 2010 | USA                       | metastatic colorectal adenocarcinoma | bevacizumab          | HAI with irinotecan or oxaliplatin/fluorouracil/leucovorin | 2.5 mg/kg          | 73          |
| Kindler        | 2010 | USA                       | pancreatic cancer                  | bevacizumab            | gemcitabine                                | 5 mg/kg           | 602         |
| Lu             | 2010 | USA, Canada               | NSCLC                             | Neovastat              | paclitaxel & carboplatin, or cisplatin & vinorelbine | 1680 ml           | 379         |
| Miles          | 2010 | UK, Australia, Canada, South Korea, Europe | breast cancer                      | bevacizumab            | docetaxel                                   | 2.5, 5 mg/kg      | 736         |
| Monk           | 2010 | USA, Peru, Argentina, Spain, France, Thailand | cervical cancer                   | pazopanib              | lapatinib                                   | 5600 mg           | 115         |
| Reck           | 2010 | Germany, Czech Republic, Poland, Canada, Russia, Switzerland, UK | NSCLC                             | bevacizumab            | gemcitabine & cisplatin                     | 2.5, 5 mg/kg      | 1043        |
| Rini           | 2010 | USA, Canada               | metastatic RCC                    | bevacizumab            | interferon alfa                            | 5 mg/kg           | 732         |
| Scagliotti     | 2010 | Italy, Germany, Hungary, Poland, Brazil, Chile, USA | NSCLC                             | sosﬁfenib             | carboplatin/paclitaxel                      | 5600 mg           | 926         |
| Serve          | 2010 | Germany                   | acute myeloid leukemia             | sosﬁfenib             | standard induction chemotherapy + consolidation therapy | 5600 mg           | 197         |
| Stathopoulos   | 2010 | Greece                    | colorectal cancer                  | bevacizumab            | irinotecan, 5-FU, leucovorin                | 2.5 mg/kg         | 222         |
| Sternberg      | 2010 | Australia, New Zealand, South Korea, Europe, South America | RCC                                | pazopanib              | none                                        | 5600 mg           | 435         |
| Tebbutt        | 2010 | Australia, New Zealand, USA | metastatic colorectal adenocarcinoma | bevacizumab            | capecitabine                               | 2.5 mg/kg         | 235         |
| Bruksy         | 2011 | USA                       | metastatic breast cancer           | bevacizumab            | taxane/gemcitabine/ capecitabine/vinorelbine | 5 mg/kg           | 684         |
| Burger         | 2011 | USA, Canada, South Korea, Japan | ovarian cancer                     | bevacizumab            | paclitaxel & carboplatin                    | 5 mg/kg           | 1873        |
| Cheouei        | 2011 | USA                       | urothelial cancer                  | vandetanib             | docetaxel                                   | 700 mg            | 142         |
| de Boer        | 2011 | Belgium, Australia, Mexico, UK, Philippines, South Africa, Italy, Germany, Taiwan | NSCLC                             | vandetanib             | pemetrexed                                  | 700 mg            | 534         |
| Guan           | 2011 | China                     | metastatic colorectal adenocarcinoma | bevacizumab            | irinotecan/S-FU/leucovorin                  | 2.5 mg/kg         | 214         |
| Hecht          | 2011 | USA, Germany, Canada, Hungary, Finland, Qatar | metastatic colorectal adenocarcinoma | PTK/ZK                 | FOLFOX 4                                   | 8750 mg           | 1168        |
| Herbst         | 2011 | USA                       | NSCLC                             | bevacizumab            | erlotinib                                   | 5 mg/kg           | 636         |
| Kato           | 2011 | Japan                     | colorectal cancer                  | cediranib              | FOLFOX6                                    | 140; 210 mg       | 172         |
| Author  | Year | Country | Type of Tumor/Macular Degeneration | VEGFi | Cointervention | VEGFi Weekly Dose | Sample Size |
|---------|------|---------|-----------------------------------|-------|---------------|------------------|------------|
| Kim     | 2011 | USA, Switzerland | Melanoma | Bevacizumab | Paclitaxel & Carboplatin | 5 mg/kg | 214 |
| Kindler | 2011 | Japan, South Korea | Pancreatic Cancer | Axitinib | Gemcitabine | 70 mg | 650 |
| Kindler | 2011 | USA, Japan, Netherlands, Canada, Germany, India | Pancreatic Cancer | Axitinib | Gemcitabine | 70 mg | 650 |
| Kudo    | 2011 | Japan | Pancreatic Cancer | Axitinib | Gemcitabine | 70 mg | 630 |
| Ohtsu   | 2011 | Japan, South Korea | Gastric Cancer | Bevacizumab | Cisplatin & Capecitabine/FU | 2.5 mg/kg | 774 |
| Perren  | 2011 | France, UK, Germany, Canada, Austria, Norway, Denmark, South Korea, USA | Ovarian Cancer | Bevacizumab | Paclitaxel & Carboplatin | 2.5 mg/kg | 180 |
| Raymond | 2011 | France, South Korea | Pancreatic Neuroendocrine Tumor | Bevacizumab | Gemcitabine | 5 mg/kg | 171 |
| Robert  | 2011 | USA, France, UK, Ukraine, Russia | Breast Cancer | Bevacizumab | Cisplatin | 5 mg/kg | 615 |
| Robert  | 2011 | USA, France, UK, Ukraine, Russia | Breast Cancer | Bevacizumab | Cisplatin | 5 mg/kg | 622 |
| Rugo    | 2011 | USA, Spain, Canada, Italy | Breast Cancer | Bevacizumab | Paclitaxel & Carboplatin | 2.5 mg/kg | 171 |
| Wells Jr | 2011 | USA, Australia | Metastatic Prostate Cancer | Bevacizumab | Prednisone | 5 mg/kg | 130 |

*These are two different trials published in the same year by the same author: Spigel et al in 2011 used bevacizumab for extensive stage small cell lung cancer in one trial and sorafenib for advanced non–small-cell lung cancer in another trial.
significantly modified the association between VEGFi treatment and the risk of mortality in meta-regression (all p > 0.08). In addition, there was no evidence from meta-regression that study risks of bias modified the association between VEGFi treatment and the risk of mortality (see eTable S5).

Cardiovascular events

Seven trials (n = 4,163), twelve trials (n = 7,864) and two trials (n = 1,153) reported the frequency of fatal or non-fatal myocardial infarction, heart failure and stroke, respectively. The pooled risk among VEGFi recipients was significantly higher for myocardial infarction, but not for heart failure or stroke (RR for myocardial infarction 3.54, 95% CI 1.61 to 7.80, I² = 0%, tau² = 0; RR for heart failure 1.63, 95% CI 0.70 to 3.79, I² = 0%, tau² = 0; RR for stroke 1.12, 95% CI 0.38 to 3.30, I² = 0%, tau² = 0; see Figure 4). The absolute magnitude of the excess risk of myocardial infarction was relatively low; the risk difference was 0.8% (control group risk = 0.3%) and number needed to harm was 125.

Thrombosis and thromboembolism

Eight trials (n = 3,747) reported the frequency of any grade thrombotic or thromboembolic events between treatment and control groups; eight trials (n = 6,244) compared the frequency of any grade arterial thrombotic or thromboembolic events; eight trials (n = 5,798) compared any grade venous thrombotic or thromboembolic events and six trials (n = 2,576) compared any or an unspecified grade of pulmonary embolism. The risk of any grade thrombotic or thromboembolic events was significantly
Figure 4. Effect of treatment with VEGFi on all-cause mortality, cardiovascular events and thrombosis.
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higher in VEGFi recipients (RR 1.53, 95% CI 1.07 to 2.20, I² = 43%, tau² = 0.11) but the absolute increase in risk was relatively low (risk difference 4%; control group risk = 8%) and number needed to harm was 25.

When individual types of thrombotic events were considered separately, the pooled risk among VEGFi recipients was significantly higher for arterial thrombotic events, but not for venous thrombotic events or pulmonary embolism (RR for arterial thrombotic events 1.80, 95% CI 1.24 to 2.59, I² = 0%, tau² = 0; RR for venous thrombotic events 1.14, 95% CI 0.87 to 1.50, I² = 33%, tau² = 0.05; RR for pulmonary embolism 1.18, 95% CI 0.51 to 2.73, I² = 48%, tau² = 0.46; see Figure 4). The absolute increase in the risk of arterial thromboembolism was relatively low (risk difference 1%; control group risk = 2%). In meta-regression,
the excess risk of thrombotic event appeared to be greater (p = 0.02) for PTK/ZK (RR 6.52, 95% CI 2.29 to 18.51) than for the other 2 VEGFi agents (bevacizumab and vandetanib, for which the pooled RR was 1.36, 95% CI 1.11 to 1.67, I² = 0%, tau² = 0). The same panel of potential explanatory variables was considered as in the meta-regression analyses on mortality. However, none significantly modified the association between VEGFi treatment and the risk of myocardial infarction or thrombosis.

Hypertension and proteinuria

Forty trials (n = 15,351) reported the incidence of hypertension. The risk of hypertension was significantly higher among VEGFi recipients (RR 3.46, 95% CI 2.89 to 4.15, I² = 58%, tau² = 0.16) (Figure 3); this corresponded to an absolute risk difference of 15% (control group risk = 6%) and number needed to harm of 7. Fourteen trials (n = 5,841) where 13 trials included bevacizumab and 1 trial included pazopanib reported the incidence of proteinuria. The pooled risk of new proteinuria was significantly higher in the VEGFi groups (RR 2.51, 95% CI 1.60 to 3.94, I² = 87%, tau² = 0.65) (Figure 3); this corresponded to a risk difference of 12% (control group risk = 8%) and number needed to harm of 8. Meta-regression did not identify any of the candidate explanatory variables as significant modifiers of the association between VEGFi treatment and hypertension or proteinuria.

Discussion

To our knowledge, this is the first meta-analysis to summarize the risk of adverse effects associated with VEGFi treatment in cancer patients. We found that the risks of fatal and nonfatal MI, hypertension, arterial thromboembolism and proteinuria were all higher among VEGFi recipients. The absolute excess risk due to VEGFi treatment varied between the different harms considered, and ranged from relatively low for myocardial infarction (absolute excess risk 0.8%; number needed to harm 125) to relatively high for new proteinuria (absolute excess risk 12%; number needed to harm 8) and hypertension (absolute excess risk 15%; number needed to harm 7). These potential harms must be considered in the context of the demonstrated benefits associated with VEGFi treatment – such as the significantly reduced risk of mortality observed in our review (absolute risk reduction 2%; number needed to treat 50). Since it is possible that timely detection of these adverse events may mitigate their clinical consequences, physicians should consider the need for follow-up measurements of blood pressure, proteinuria and new symptoms of cardiovascular disease – especially in those at higher baseline vascular risk.

Although VEGFi appear to increase the risk of myocardial infarction, we found no convincing evidence that (as a class) they increase the likelihood of heart failure or stroke. Previous authors have speculated that VEGFi might cause cardiotoxicity through their effects on blood pressure, or alternatively by blocking PDGFR signalling [25]. Similarly, we found an association between VEGFi use and the risk of arterial thromboembolic events, but not with the risk of venous thrombosis, which is generally more common. The link between VEGF inhibition and hypercoagulability is plausible, because VEGFi may expose platelets and coagulation factors (such as von Willebrand factor) to subendothelial procoagulant phospholipids – leading to activation of the hemostatic system [19].

We also found that VEGFi treatment substantially increased the risk of new proteinuria – with one excess case for every 8 patients treated. Of 14 trials that reported on incident proteinuria, 13 used bevacizumab, making it uncertain whether the conclusions can be generalized to other agents. VEGFi-induced proteinuria might result from acute hypertension [8], and also from direct effects of VEGF antagonism on the glomerulus. VEGF is an important determinant of normal glomerular function [26], and experimental models show that blocking renal VEGF results in down-regulation of tight junction proteins such as nephrin, with consequent proteinuria [21,27,28].

We did not find an increase in the risk of all-cause mortality due to VEGFi treatment, perhaps because increased risk of death due to vascular events is offset by lower risk of death due to cancer. An interaction between chemotherapy co-intervention and total mortality risk (p = 0.007) might be because some participants received chemotherapy to treat or palliate very advanced cancer. Alternatively, VEGFi such as bevacizumab might interact unfavourably with certain chemotherapeutic agents, increasing the risk of adverse events [29].

To our knowledge, this is the first systematic review of randomized trials that examines the adverse events caused by VEGFi in cancer patients. Prior reviews have focused on the risk of bleeding [30,31] or venous thromboembolic events [32]; others have been limited to studies of specific cancers [10,30,33–36] or a particular agent [29]. The consistency of our results regardless of the type of cancer or agent studied argues in favour of a more inclusive approach. Our analysis has several important strengths, including the use of a comprehensive search strategy, as a large search yield (72 analyses studying 11 different VEGFi) and rigorous methods including meta-regression. Finally, we included only randomized controlled trial to reduce the risk of bias.

However, our study has some limitations that should be considered. First, the pooled trials were clinically heterogeneous – including variations in cancer type, VEGFi studied, inclusion/exclusion criteria, study risks of bias, and the treatment strategies used. However, metaregression found little evidence that these differences modified the effect of VEGFi on the outcomes of interest. Second, although there was little statistical heterogeneity of effect for the analyses linking VEGFi with the risk of myocardial infarction or arterial thromboembolism, there was statistical heterogeneity in the magnitude of the excess risk of hypertension and proteinuria. Although the statistical heterogeneity makes it difficult to confidently estimate the precise magnitude of the excess risk, it does not threaten our conclusions: 39/40 trials and 13/14 randomized trials that examines the adverse events caused by VEGFi treated. Of 14 trials that reported on incident proteinuria, 13 used bevacizumab, making it uncertain whether the conclusions can be generalized to other agents. VEGFi-induced proteinuria might result from acute hypertension [8], and also from direct effects of VEGF antagonism on the glomerulus. VEGF is an important determinant of normal glomerular function [26], and experimental models show that blocking renal VEGF results in down-regulation of tight junction proteins such as nephrin, with consequent proteinuria [21,27,28].
studies published in English. However, since many trials were international (and most cancer trials are published in English), this is unlikely to have affected our conclusions. Also, we did not consider other outcomes such as bleeding [31,37–40] or delayed wound healing complications [41,42] but this would less likely to change our inferences about mortality or other included outcomes. Finally, although inclusion of only randomized trials likely strengthened the internal validity of our conclusions, it may have reduced generalizability. The risk of cardiac events attributable to VEGFi treatment was larger in observational studies than in randomized trials – perhaps because of the select nature of trial participants. Since the risk of adverse events tends to be higher in “real world” patients, it is likely that our analyses of absolute excess risks have underestimated their true incidence.

In conclusion, VEGFi increase the risk of potentially important adverse effects in people with cancer, including myocardial infarction, arterial thromboembolism, hypertension, and new proteinuria. These harms should be considered in the context of the known benefits of VEGFi for the treatment of cancer.

Supporting Information

eTable S1 Search strategies. (DOC)
eTable S2 VEGFi classification. (DOC)
eTable S3 Details of the studies. (DOC)
eTable S4 Study risks of bias assessment. (DOC)

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