Bevacizumab increases the risk of arterial ischemia: a large study in cancer patients with a focus on different subgroup outcomes

F. A. B. Schutz¹, Y. Je², G. R. Azzi¹, P. L. Nguyen¹ & T. K. Choueiri¹*

¹Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School; ²Department of Nutrition, Harvard School of Public Health, Boston, USA

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Background: Bevacizumab, a humanized monoclonal antibody targeting the vascular endothelial growth factor, is a therapeutic agent used in a variety of neoplasms. We did a meta-analysis of randomized controlled trials to fully characterize the arterial thromboembolic events (ATEs) risk with bevacizumab in certain patients’ subgroups.

Materials and Methods: We carried out a literature search on Medline for randomized trial reported from January 1966 to December 2009. Abstracts presented at the American Society of Clinical Oncology held between 2004 and 2009 were also searched for relevant clinical trials. Summary incidence, relative risks (RRs) and 95% confidence intervals (CIs) were calculated using random-effects or fixed-effects models based on the heterogeneity of included studies.

Results: A total of 13 026 patients from 20 randomized trials were included in the meta-analysis. Overall RR for ATE with bevacizumab-based therapy versus controls was 1.46 (95% CI 1.11–1.93, P = 0.007). On subgroup analysis, no significant risk differences were found based on the type of malignancy, type of clinical trial (phase II or III trials), type of publication (full papers versus presentations), high- versus low-dose bevacizumab and early versus advanced disease trials. When stratified by concomitant therapies, we found that gemcitabine-based regimens had a significant lower ATE risk compared with non-gemcitabine regimens (P = 0.01).

Conclusions: Bevacizumab treatment is associated with a significant increase in the risk of arterial thrombosis. Our results seem to be generalizable to the vast majority of patients receiving bevacizumab in multiple settings.

Key words: arterial thromboembolic events, bevacizumab, ischemia, meta-analysis, monoclonal antibody, myocardial infarction

introduction

Bevacizumab, a recombinant humanized monoclonal antibody targeting the vascular endothelial growth factor (VEGF), is an anti-angiogenic drug used widely in the treatment of various neoplasms. Based on a significant clinical benefit, bevacizumab is currently Federal and Drug Administration approved for treatment of advanced colorectal cancer (CRC) (in combination with 5-fluorouracil-based chemotherapy), advanced non-small-cell lung cancer (NSCLC) (in combination with carboplatin and paclitaxel chemotherapy), advanced breast cancer (in combination with paclitaxel chemotherapy), glioblastoma (as a single agent) and metastatic renal cell carcinoma (RCC) (in combination with interferon-α) [1]. It is also under investigation for the treatment of many other cancers with, as of February 2010, >500 registered active clinical studies with bevacizumab-containing regimens listed on the National Cancer Institute website [2]. Bevacizumab was the first agent in a series of new anti-VEGF targeted therapies, with sunitinib, sorafenib and pazopanib, three novel tyrosine kinase inhibitors targeting the VEGF receptor. Targeted therapies as opposed to classical cytotoxic treatments hold the promise of less systemic toxicity while having an improved ‘selective’ antitumor efficacy [3]. Nevertheless, several other toxic effects have been linked with the use of bevacizumab, including hypertension, gastrointestinal perforations, wound healing complications, fistulas (both gastrointestinal and non-gastrointestinal), reversible posterior leukencephalopathy and proteinuria [1]. In 2007, a pooled analysis of five industry-sponsored randomized controlled trials (RCTs) with a total of 1745 patients showed that bevacizumab increases the risk or arterial thrombosis [4]. More recently, Ranpura et al. carried out a meta-analysis of bevacizumab-treated patients, showing an increased risk of ATE with the highest incidence being in RCC and CRC [5]. Our group also sought to carry out a large comprehensive up-to-date meta-analysis that focused particularly on different subgroup outcomes, in order to characterize which patient populations are at particular higher risk for arterial thrombosis from bevacizumab.
materials and methods

selection of studies

We reviewed PubMed citations from January 1966 to December 2009. The search criteria included only clinical trials and the keyword ‘bevacizumab’ or ‘avastin’. We only reviewed articles published in the English language. We also searched abstracts and virtual meeting presentations from the American Society of Clinical Oncology (ASCO) (http://www.asco.org/ASCO) conferences, which took place between January 2004 and December 2009, using the keywords ‘bevacizumab’ or ‘avastin’ and ‘randomized’. When more than one publication was identified from the same clinical trial, we used the most recent or complete report of that trial. An independent search using the citation database Web of Science (developed by the Institute for Scientific Information) also was carried out to ensure that no clinical trials were missed. The most recent bevacizumab package insert was also accessed to identify relevant information.

data extraction and clinical end points

Data extraction was conducted independently by three investigators (TKC, FABS and GRA) according to the Quality of Reporting of Meta-analyses (QUORUM) guidelines [6], and any discrepancies between reviewers were resolved by consensus. For each study, we extracted the following information: first author’s name, year of publication, trial phase, underlying malignancy, number of enrolled subjects, treatment arms, number of cases in experimental and control arms, median age, median follow-up, median treatment duration, median progression-free survival, bevacizumab dose and reported arterial thrombotic events.

The following adverse outcomes were considered as ATE and were included in the analyses: arterial thrombosis, cerebral infarct, cerebral ischemia, cerebrovascular accident, myocardial infarction, myocardial ischemia and acute coronary syndrome. Trials that met the following criteria were included in our analysis: randomized phase II, phase III trials, patients assigned to treatment with bevacizumab in only one arm and adequate safety data available for ATE.

statistical analysis

For the calculation of incidence and relative risks (RRs) for each trial, the number of ATEs and the number of patients from each arm (bevacizumab and control arms) were extracted from the safety profile. The proportion of patients with those adverse outcomes and 95% confidence intervals (CIs) were derived from each trial. We also calculated RRIs and CIs of ATE in patients assigned to bevacizumab versus controls in the same trial. For studies reporting zero ATE events in a treatment or control arm, yet an informative trial as a whole, we applied a classic half-integer continuity correction to compute the RR and variances.

To calculate the overall incidence or RRs of ATEs, we pooled study-specific estimates using both the fixed-effects model (weighted with inverse variance) and the random-effects model proposed by Dersimonian and Laird that considers both within-study and between-study variations [7]. Statistical heterogeneity between trials included in the meta-analysis was assessed using the Cochrane’s Q statistic, and inconsistency was quantified with the I² statistic [100% × (Q − df)/Q] that estimates the percentage of total variation across studies due to heterogeneity rather than chance [8]. The assumption of homogeneity was considered invalid for P-values <0.1, and the result from random-effects model was presented when a significant heterogeneity was found.

To explore the possible reasons for the heterogeneity, we conducted subgroup analyses by underlying malignancy, bevacizumab dose, type of trial (abstract versus full paper or randomized phase II versus phase III), disease stage (adjuvant versus metastatic setting) and concomitant anti-angioplastic therapy type. To test for variation in risk estimates by those variables, we conducted meta-regression analyses. In addition, we conducted sensitivity analyses by omitting one study at a time to see the influence of each trial on the overall effect estimate. Finally, publication bias was evaluated through funnel plots (i.e. plots of study results against precision) and with the Beggs and Egger’s tests [9, 10]. A two-tailed P-value of <0.05 was considered statistically significant. All statistical analyses were carried out by using Stata version 9.2 software (Stata Corporation, College Station, TX).

role of the funding source

This study was funded by the philanthropic Trust Family Research Fund for Kidney Cancer. The authors had access to all the raw data and had the final responsibility for the decision to submit the manuscript for publication.

results

population characteristics

Our search yielded a total of 148 potentially relevant studies, 100 PubMed published papers and 48 abstracts from ASCO meetings proceedings. After evaluating each reference, 83 were excluded due to one of the following reasons: non-cancer trials, trials with bevacizumab in both arms, editorials, letters, commentaries and review articles. Subsequently, we carefully evaluated each one of the remaining 65 trials and excluded an additional 45 trials due to duplicate reports or absence of adequate safety data profile. Therefore, 20 trials were selected for inclusion in the meta-analysis, 16 published papers [11–26] and 4 presentations at the ASCO meetings [27–30]. The selection process is represented in Figure 1.

The baseline characteristics of each trial are presented in Table 1. The concomitant therapies with bevacizumab included several chemotherapeutic agents (majority based on platinum, fluoropyrimidines or taxanes) or immunotherapy (interferon-α). All trials, except one [12], included patients with metastatic disease.

A total of 13026 patients from 20 RCTs were available for the meta-analysis. All selected trials usually included patients with adequate organ function, coagulation and hematologic parameters. Patients with uncontrolled hypertension or clinically significant cardiovascular or cerebrovascular events or disease during the preceding 6–12 months were typically excluded from these trials. The most treatment-related reported event was ‘ATE’ (without further details), followed by cerebrovascular ischemic events and cardiac ischemic events.

incidence of ATEs

Among the 7157 patients who received bevacizumab, 159 presented with ATE. Using a random-effects model for this analysis (heterogeneity test: Q = 54.446, P < 0.001, I² = 65%), the summary incidence of ATEs was 2.6% (95% CI 2.0–3.5).

The incidence was stratified according to the type of malignancy (Table 2). Two trials included RCC, eight included CRC, four included NSCLC, three included breast cancer, two included pancreatic cancer and one included mesothelioma. The highest ATE incidence was observed in CRC patients, with 3.2% (95% CI 1.9%–5.4%), whereas the lowest was in breast cancer, 0.7% (95% CI 0.1%–3.6%).
The RR of high-grade ATE was calculated. One hundred fifty-nine events were observed among 7157 bevacizumab-treated patients, whereas there were 78 events among 5869 patients from control arms. The overall RR was 1.46 (95% CI 1.11–1.93, \( P = 0.007 \)). No significant heterogeneity between the included trials was observed (\( Q = 21.486, P = 0.311, I^2 = 12% \)). The results are detailed in the forest plot in Figure 2.

As an exploratory analysis, stratified analysis was done based on the underlying malignancy. The highest risk of ATE was observed among RCC patients (RR 3.95; 95% CI 1.1–14.5, \( P = 0.035 \)).

Metastatic breast cancer patients, pancreatic cancer patients and mesothelioma patients also presented an increased risk of ATE (RR > 1) but did not reach statistical significance (Table 2). When compared against NSCLC, patients with other histologies had a significant increase in the risk of ATE (RR 1.78; 95% CI 1.29–2.44, \( P < 0.001 \)), and the difference against NSCLC was statistically significant (\( P = 0.030 \)). There was not any other significant difference between the different histological subgroups.

We also attempted to calculate the RR for the early (adjuvant) versus advanced disease trials. Only one trial included patients with early-stage disease (stage II and III CRC) \[12\]. The RR for the adjuvant trial was 1.38 (95% CI 0.76–2.52), and RR for the advanced disease trials was 1.49 (95% CI 1.09–2.03) with no significant difference (\( P = 0.764 \)).

In order to analyze the influence of the bevacizumab treatment duration, we stratified the patients between short and long treatment duration. Fifteen trials provided information about the treatment duration. The mean of the median treatment durations was 4.8 months. The incidence of ATE was 2.8% (95% CI 2.0–4.0) and 2.3% (95% CI 1.7–3.2) for trials with long (\( \geq 4.8 \) months) and short (<4.8 months) treatment duration, respectively, with no significant differences (\( P = 0.417 \)).

Quality of the study

Fourteen trials included in this analysis were randomized phase III trials, while the remaining 6 trials were randomized phase II trials. Half of the trials had placebo double-blind controlled arms. The results of four trials were presented in ASCO.
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Phase</th>
<th>Histology</th>
<th>Patients enrolled</th>
<th>Treatment arms</th>
<th>Median follow-up (months)</th>
<th>Median age (years)</th>
<th>Median treatment duration (months)</th>
<th>Median progression-free survival (months)</th>
<th>Patients for analysis</th>
<th>ATE number</th>
<th>Bevacizumab dose (mg/week)</th>
<th>Reported ATE events</th>
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</thead>
<tbody>
<tr>
<td>Escudier, 2007</td>
<td>III</td>
<td>RCC</td>
<td>649</td>
<td>INF + BEV HD</td>
<td>13.3</td>
<td>61</td>
<td>9.7</td>
<td>10.2</td>
<td>337</td>
<td>5</td>
<td>5</td>
<td>ATE</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>INF + placebo</td>
<td>12.8</td>
<td>60</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mFOLFOX6 + BEV</td>
<td>35.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>41.9%</td>
<td>11.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR</td>
<td>1326</td>
<td>25</td>
<td>2.5</td>
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</tr>
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<td>Allegra, 2009</td>
<td>III</td>
<td>CRC</td>
<td>2710</td>
<td>mFOLFOX6</td>
<td>41.7%</td>
<td>(260 years)</td>
<td>6</td>
<td>NR</td>
<td>1321</td>
<td>18</td>
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<td>NSCLC</td>
<td>1043</td>
<td>GC + BEV LD</td>
<td>NR</td>
<td>57</td>
<td>4.9</td>
<td>6.7</td>
<td>330</td>
<td>8</td>
<td>2.5</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>GC + BEV HD</td>
<td>59</td>
<td>4.4</td>
<td>6.5</td>
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<td>329</td>
<td>10</td>
<td>5</td>
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<td></td>
<td>GC + placebo</td>
<td>59</td>
<td>3.5</td>
<td>6.1</td>
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<td>327</td>
<td>15</td>
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<td>III</td>
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<td>61</td>
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<td>1401</td>
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<td>694</td>
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<td>FOLFOX4 + BEV HD</td>
<td>28&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>FU-LV or IFL + BEV LD</td>
<td>NR</td>
<td>59.5</td>
<td>10.1</td>
<td>10.6</td>
<td>501</td>
<td>20</td>
<td>2.5</td>
<td>ATE&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>III</td>
<td>mBC</td>
<td>722</td>
<td>IFL + placebo</td>
<td>59.2</td>
<td>6.9</td>
<td>6.2</td>
<td></td>
<td>396</td>
<td>5</td>
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<td>Van Cutsem, 2009</td>
<td>III</td>
<td>Pancreatic cancer</td>
<td>607</td>
<td>Paclitaxel + BEV HD</td>
<td>41.6</td>
<td>56</td>
<td>7.1</td>
<td>11.8</td>
<td>365</td>
<td>7</td>
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<td>Cerebrovascular ischemia</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Paclitaxel</td>
<td>43.5</td>
<td>55</td>
<td>5.1</td>
<td>5.9</td>
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<tr>
<td>Price, 2008</td>
<td>III</td>
<td>CRC</td>
<td>471</td>
<td>CAP ± MMC + BEV LD</td>
<td>NR</td>
<td>57</td>
<td>NR</td>
<td>NR</td>
<td>315</td>
<td>16</td>
<td>2.5</td>
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<td>Kabbinavar, 2005</td>
<td>II</td>
<td>CRC</td>
<td>209</td>
<td>CAP + FU-LV + BEV LD</td>
<td>NR</td>
<td>71.3</td>
<td>7.75</td>
<td>9.2</td>
<td>161</td>
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<td>CAP + FU-LV + placebo</td>
<td>70.7</td>
<td>5.75</td>
<td>5.5</td>
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<td>Treatment arms</td>
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<td>Median age (years)</td>
<td>Median treatment duration (months)</td>
<td>Median progression-free survival (months)</td>
<td>Patients for analysis</td>
<td>ATE number</td>
<td>Bevacizumab dose (mg/week)</td>
<td>Reported ATE events</td>
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<tr>
<td>Kabbinavar, 2003 II</td>
<td>CRC</td>
<td>104</td>
<td>FU-LV + BEV LD</td>
<td>NR NR NR</td>
<td>9.0&lt;sup&gt;d&lt;/sup&gt;</td>
<td>7.2</td>
<td>5.2</td>
<td></td>
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<td>NSCLC</td>
<td>122</td>
<td>PMX or DTX + BEV HD</td>
<td>15.8&lt;sup&gt;b&lt;/sup&gt; 63.5</td>
<td>NR</td>
<td>4.8</td>
<td></td>
<td>39</td>
<td>0</td>
<td>5</td>
<td>ATE</td>
<td></td>
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<tr>
<td>Miller, 2005 II</td>
<td>mBC</td>
<td>462</td>
<td>CAP + BEV HD CAP</td>
<td>NR 51 NR</td>
<td>4.86</td>
<td>4.17</td>
<td></td>
<td>229</td>
<td>1</td>
<td>5</td>
<td>ATE&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Johnson, 2004 II</td>
<td>NSCLC</td>
<td>99</td>
<td>CP + BEV LD/HD CP</td>
<td>NR NR 6–7.5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4.3–7.4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4.5</td>
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<td>66</td>
<td>3&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>ATE&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td>Moehler, 2009 II</td>
<td>CRC</td>
<td>46</td>
<td>CAPIRI + BEV LD CAPIRI</td>
<td>17.0 60</td>
<td>6</td>
<td>12.8</td>
<td></td>
<td>29</td>
<td>1</td>
<td>2.5</td>
<td>Myocardial infarction,</td>
<td></td>
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<td>Miles, 2008 III</td>
<td>mBC</td>
<td>736</td>
<td>Docetaxel + BEV LD Docetaxel + placebo</td>
<td>10.2&lt;sup&gt;b&lt;/sup&gt; 54</td>
<td>54</td>
<td>8.7</td>
<td></td>
<td>250</td>
<td>0</td>
<td>2.5</td>
<td>ATE</td>
<td></td>
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<tr>
<td>Sandler, 2006 III</td>
<td>NSCLC</td>
<td>878</td>
<td>CP + BEV HD CP</td>
<td>19 43% (265 years)</td>
<td>5.25</td>
<td>6.4</td>
<td></td>
<td>420</td>
<td>8&lt;sup&gt;f&lt;/sup&gt;</td>
<td>5</td>
<td>ATE</td>
<td></td>
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<tr>
<td>Kindler, 2007 III</td>
<td>Pancreatic cancer</td>
<td>602</td>
<td>GEM + BEV HD GEM + placebo</td>
<td>11.3 63.8</td>
<td>3.9</td>
<td>6.9</td>
<td></td>
<td>277</td>
<td>6</td>
<td>5</td>
<td>Cerebrovascular accident</td>
<td></td>
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<tr>
<td>Karrison, 2007 III</td>
<td>Mesothelioma</td>
<td>106</td>
<td>GC + BEV HD GC + placebo</td>
<td>NR 62</td>
<td>5.25</td>
<td>6.9</td>
<td></td>
<td>53</td>
<td>1</td>
<td>5</td>
<td>Cerebrovascular accident</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Median treatment duration reported only for bevacizumab and/or placebo, the cemotherapy and/or immunotherapy had other median treatment durations.  
<sup>b</sup>Median follow-up reported for the entire cohort.  
<sup>c</sup>Data for the number of ATE extracted from previous analysis of industry-sponsored randomized controlled trials [5].  
<sup>d</sup>Only time to treatment progression (TTP) reported in the manuscript.  
<sup>e</sup>Number of ATE, median treatment duration and median progression-free survival reported for the bevacizumab HD and LD combined cohorts.  
<sup>f</sup>Data retrieved from the presentation in the American Society of Clinical Oncology meeting in 2005.

ATE, arterial thromboembolic event; RCC, renal cell cancer; INF, interferon; BEV, bevacizumab; HD, high-dose; CRC, colorectal cancer; mFOLFOX6, modified FOLFOX6 (fluorouracil, leucovorin and oxaliplatin) regimen; LD, low-dose; CNS, central nervous system; NSCLC, non-small-cell lung cancer; FOLFIRI, irinotecan, fluorouracil and leucovorin regimen; XELOX, capecitabine and oxaliplatin regimen; FU, fluorouracil; LV, leucovorin; IFL, irinotecan, fluorouracil and leucovorin regimen; mBC, metastatic breast cancer; GEM, gemcitabine; CAP, capcitabine; MMC, mytomycin C; PMX, pemetrexed; DTX, docetaxel; CAPIRI, capcitabine and irinotecan regimen; CP, carboplatin and paclitaxel regimen; GC, gemcitabine and cisplatin regimen.
meetings only, so far. For quality analysis purpose, we attempted to look at differences in incidence or RR of congestive heart failure based on the type of report (full paper versus ASCO meeting presentation), randomized trial type (II versus III) or placebo controlled/double-blind versus non-placebo controlled/double-blind. No statistically significant differences were found (results not shown).

influence of bevacizumab dose

The ATE incidence and risk was also stratified based on two bevacizumab dosages: 2.5 or 5 mg/week. Ten trials randomized patients to low-dose treatment and 12 trials to the high-dose bevacizumab (Table 2). The incidence of ATE was 3.2% (95% CI 2.1%–4.9%) and 2.1% (95% CI 1.6%–2.7%), respectively, for the low- and high-dose groups. The overall RR for the low and high dose was 1.41 (95% CI 1.02–1.96) and 1.32 (95% CI 0.83–2.11), respectively, with no statistically significant difference among both groups (P = 0.948).

influence of concomitant treatment

Agents such as gemcitabine, fluoropyrimidines, cisplatin and interferon have been associated with an increase in the risk of arterial events [31–35]. Therefore, we attempted to evaluate the influence of the concomitant treatments with bevacizumab stratifying the analysis depending on the chemotherapy or immunotherapy used. The trials were stratified based on the following regimens: platinum, fluoropyrimidines, taxanes, gemcitabine and interferon. Only studies with gemcitabine chemotherapy as a backbone had significantly lower risk of ATE (RR 0.82; 95% CI 0.50–1.33) when compared with the non-gemcitabine subgroup (RR 1.92; 95% CI 1.38–2.69), with P-value for difference = 0.011.

sensitivity analysis

In order to examine the influence of each trial on the overall RR, we conducted a sensitivity analysis by omitting one study at a time. By doing that, we observed that the trial of Reck et al.

Table 2. Incidence and RR of ATE events with bevacizumab among patients with various tumor types and different bevacizumab dose (2.5 or 5.0 mg/kg)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of studies</th>
<th>ATE no./total no.</th>
<th>Incidence (95% CI), %</th>
<th>RR (95% CI), P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>20</td>
<td>159/7157</td>
<td>78/3869</td>
<td>2.6 (2.0–3.5)</td>
</tr>
<tr>
<td>Stratified by malignancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>2</td>
<td>15/703</td>
<td>3/653</td>
<td>2.3 (1.4–3.7)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>8</td>
<td>91/3553</td>
<td>39/2989</td>
<td>3.2 (1.9–5.4)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>3</td>
<td>8/1091</td>
<td>2/794</td>
<td>0.7 (0.1–3.6)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>2</td>
<td>15/573</td>
<td>13/550</td>
<td>2.6 (1.6–4.4)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>4</td>
<td>29/1184</td>
<td>21/828</td>
<td>2.5 (1.8–3.7)</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>1</td>
<td>1/53</td>
<td>0/55</td>
<td>1.9 (0.3–12.2)</td>
</tr>
<tr>
<td>Stratified by bevacizumab dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>10</td>
<td>102/3876</td>
<td>62/3551</td>
<td>3.2 (2.1–4.9)</td>
</tr>
<tr>
<td>High dose</td>
<td>12</td>
<td>54/3215</td>
<td>32/2881</td>
<td>2.1 (1.6–2.7)</td>
</tr>
</tbody>
</table>

ATE, arterial thromboembolic event; CI, confidence interval; RR, relative risk; NSCLC, non-small-cell lung cancer.

Figure 2. Relative risk (RR) of Arterial Thromboembolism Associated With Bevacizumab versus Control

Table 2. Incidence and RR of ATE events with bevacizumab among patients with various tumor types and different bevacizumab dose (2.5 or 5.0 mg/kg)
[13] had a significant impact on the overall RR. Therefore, when eliminating that trial, the summary risk for ATE for the remaining 19 trials became more significant (RR 1.75; 95% CI 1.30–2.38, \( P < 0.001 \)).

**publication bias**

No evidence of publication bias was detected for RR of ATE of this study by either the Begg’s test or the Egger’s test (Begg’s test, \( P = 0.77 \); Egger’s test, \( P = 0.23 \)).

**discussion**

This large up-to-date comprehensive meta-analysis from studies in the literature confirms the risk of ATE associated with bevacizumab treatment. One prior study was based on a pooled analysis of five industry-sponsored trials totaling 1745 only and three types of cancers (CRC, NSCLC and breast cancer) [4], compared with >13 000 patients and six types of cancers (additional cancers: RCC, mesothelioma and pancreatic cancer) in the current study. Another recently published meta-analysis validates our results and finds a 44% increase in the risk of ATE, in line with 46% risk we found [5]. Similarly, we found an increased risk for RCC and CRC, with no effect from the dose of bevacizumab on the risk of ATE. Nevertheless, our study differs from the one by Ranpura et al. in several aspects: (i) we included patients from studies up to December 2009 and included a higher number of patients, (ii) we carried out a much more extensive subgroup analyses, (iii) we did not differentiate between high- and all-grade ATE, as very few studies reported on all-grade or low-grade ATE and since the vast majority of ATE events are in general of serious consequences and frequently necessitate hospitalizations, (iv) we carried out sensitivity analysis to assess the impact of each study on the overall RR for ATE.

Meta-regression analysis showed that there is no significant difference in risk based on the type of clinical trial (phase II or III trials), type of publication (full papers versus presentations), dose of bevacizumab and early versus advanced disease trials. The absence of difference in risk for low- versus high-dose bevacizumab indicated that the ‘low dose’ may be already reaching the saturation level to promote clotting. Regarding the stratification by concomitant therapies, we found that gemcitabine-based regimens had a significant lower ATE risk compared with non-gemcitabine regimens. We also observed a lower risk for NSCLC when compared with non-NSCLC. According to the sensitivity analysis, these results were potentially influenced by the trial of Reck et al., where NSCLC patients treated with gemcitabine chemotherapy had an RR for ATE <1. Another explanation would be that gemcitabine was used usually in NSCLC or pancreatic cancer patients, and those patients have usually shorter treatment durations due to the usually short progression-free survival.

We attempted to analyze the impact of treatment duration on the incidence of the thrombotic events, similar to another study showing that the majority of ATEs occur the first 3 months of therapy [4], but the data regarding the occurrence of the event in the course of the trial was frequently not reported. We also calculated the mean median treatment duration of the included trials and compared the incidence of ATE between those trials with longer or shorter treatment duration, but no difference was observed. Ideally, only individual patient data would allow us to clarify this issue.

It is important to remember that typical randomized phase II or III drug development studies have tight inclusion and exclusion criteria and often rigorous treatment plans in order to ensure the integrity of the data by filtering out unfit patients [36]. Therefore, randomized trials from our report rarely included patients with baseline significant cardiovascular risk factors, such as poorly controlled hypertension, diabetes or prior history of cardiovascular events. It is conceivable that ATE incidence could be even higher in a real-life setting with an older population with underlying vascular comorbidities. The report by Scapaticci et al. using individual patients data and post hoc analyses clearly showed that ATEs were essentially associated with a history of prior ATE (\( P < 0.001 \)) or age of 65 years or older (\( P = 0.01 \)) [4].

Whether the combination of bevacizumab to cytotoxic chemotherapy (or a specific cytotoxic agent) leads to an enhanced thrombotic risk as compared with bevacizumab alone is not well defined. While the interaction between cancer, cytotoxic chemotherapy and thrombosis is well documented, the thrombotic risk includes mainly venous rather than arterial events, although arterial events have been reported [37]. The fact that the ATE risk was also increased in patients treated with bevacizumab and immunotherapy (rather than traditional cytotoxic chemotherapy) points to the fact that bevacizumab is likely to be the main culprit in for ATE events rather than an interaction between chemotherapy and bevacizumab.

It is important to point out that death or significant disability from ATE was not captured in the studies analyzed and, therefore, the impact of bevacizumab on this aspect cannot be determined. Nevertheless, the vast majority of ATEs are myocardial infarctions and cerebral vascular events, which are in general of serious consequences.

The mechanism behind bevacizumab increasing the risk of ATE has been mostly linked to a pathologic perturbation at the level of the endothelial cell mediated by VEGF depletion. The endothelial cell plays a critical role in vascular homeostasis and VEGF provides a vascular protective effect on the endothelial cell effect through anti-apoptosis, anti-inflammation and survival [38]. VEGF is also known to increase nitric oxide (NO) production by endothelial cells with resulting antiplatelet actions and inhibition of leukocyte adhesion [39, 40]. As a result, a VEGF inhibitor such bevacizumab can disrupt endothelial cell function and cause vascular wall defects exposing pro-thrombotic phospholipids on the luminal plasma membrane and the underlying matrix, leading to arterial thrombosis [41]. Furthermore, an interesting study from Meyer et al. showed that in animal models, bevacizumab can independently induce platelet aggregation, degranulation and thrombosis through complex formation with VEGF and activation of the platelet Fcgamma RIIA IgG receptor [42].

As a conclusion, we found that bevacizumab use is associated with a significant increase in the risk of arterial thrombosis, in line with other reports. Most of our subgroups analyses suggest that our results can be extended to the vast majority of patients receiving bevacizumab in multiple settings. Clinicians should...
be aware of the possibility of increased ATE, especially in patients at higher risk and side-effects of VEGF inhibitors such as bevacizumab warrant continued surveillance by healthcare providers.

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**disclosure**

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**references**


