Cardiovascular Adverse Events in Patients With Cancer Treated With Bevacizumab: A Meta-Analysis of More Than 20 000 Patients

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***Background*—**The monoclonal antibody bevacizumab effectively inhibits angiogenesis in several types of cancers by blocking vascular endothelial growth factor. However, life-threatening cardiovascular adverse effects could limit its use and may warrant specific follow-up strategies.

***Methods and Results*—**We systematically searched MEDLINE, Cochrane, EMBASE, and Web of Science for randomized controlled trials published until November 2016 that assessed patients with cancer treated with or without bevacizumab in addition to standard chemotherapy. A total of 20 050 patients with a broad range of cancer types from 22 studies were included in this analysis (10 394 in the bevacizumab group and 9656 in the control group). The risks of arterial and venous adverse events were higher in the bevacizumab groups (relative risk [RR], 1.37; 95% CI, 1.10–1.70 [P=0.004] and RR, 1.29; 95% CI, 1.12–1.47 [P<0.001], respectively), and more arterial adverse events occurred in patients taking high-dose bevacizumab regimens. Bevacizumab treatment was associated with the highest risk of cardiac and cerebral ischemia in the high-dose bevacizumab groups (RR, 4.4; 95% CI, 1.59–12.70 [P=0.004] and RR, 6.67; 95% CI, 2.17–20.66 [P=0.001], respectively). In addition, the risk of bleeding and arterial hypertension were higher in the bevacizumab groups (RR, 2.74; 95% CI, 2.38–3.15 [P<0.001] and RR, 4.73; 95% CI, 4.15–5.39 [P<0.00001], respectively), with higher values for patiens taking high-dose regimens.

***Conclusions*—**Treatment with bevacizumab increases the risk of arterial adverse events, particularly cardiac and cerebral ischemia, venous adverse events, bleeding, and arterial hypertension. This risk is additionally increased with high doses of bevacizumab. Further studies should determine the appropriate options for cardio-oncology management.

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Key Words: bevacizumab • cardio-oncology • cardiovascular adverse events

In the past few decades, substantial progress has been made in the treatment of patients with oncologic conditions, particularly in the field of targeted therapies using specific antibodies.[1] However, despite the prolonged survival rates associated with therapy, concerns have been raised regarding the adverse effects of these novel drugs.[2–6] Therefore, it is imperative to establish a comprehensive oncocardiologic management strategy for these patients.[7]

Among the most frequently prescribed novel antibodies is bevacizumab—a master regulator of tumor angiogenesis.[8] Bevacizumab is a monoclonal antibody that binds to the vascular endothelial growth factor (VEGF) A ligand, which is thought to play a dominant role in regulating angiogenesis in cancerous cells.[9] Currently, bevacizumab is approved by the European Medicines Agency for the treatment of colorectal carcinoma; breast cancer; non–small cell lung cancer; renal cell cancer; ovarian, fallopian tube, or primary peritoneal cancer; and carcinoma of the cervix.[10] Furthermore, the US Food and Drug Administration has approved bevacizumab for the treatment of glioblastoma.[11] For patients with metastatic colorectal cancer, it was estimated that bevacizumab was prescribed for 54% of patients as an initial first-line treatment, for 58% of patients who needed a continued second-line regimen, and for 50% of patients as third-line therapy.[12]

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Accompanying Table S1 and Figures S1 through S3 are available at http://jaha.ahajournals.org/content/6/8/e006278/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- The study combines data from 22 randomized controlled trials with 20 050 patients treated with bevacizumab on top of standard chemotherapy versus chemotherapy alone and makes an extensive assessment of the subtypes of arterial adverse events, subtypes of cancer, and impacts of different dosages and follow-up times on outcomes.

What Are the Clinical Implications?

- Because of the life-threatening impact of severe cardiovascular adverse events, our findings are of substantial importance for the daily care of patients with cancer and could contribute to the advancement of treatment protocols, with particular emphasis on cardiovascular surveillance, prevention, and multidisciplinary decisions in cardio-oncology teams.

There is a rapidly growing body of evidence demonstrating the efficacy of bevacizumab in prolonging survival by decreasing tumor growth and improving the delivery of cytotoxic drugs to neoplastic cells. However, randomized controlled trials (RCTs) have reported cardiovascular adverse events that are not fully characterized.[13–18] A complete analysis would include a precise evaluation of the type of adverse event (arterial/venous event, cardiac ischemia, or cerebral ischemia), determination of coexisting risk factors, assessment of dose dependency, and determination of whether a high-dose bevacizumab regimen poses a higher relative risk than a low-dose regimen.[19–23] Furthermore, with the exception of RCTs from recent years, previous analyses focused primarily on colorectal cancer, included a broad range of tumors, and reported only the sum of adverse, and particularly arterial, events without a detailed focus on the type of cardiovascular damage.[5,6,24]

Given that the overall rate and risk of cardiac and cerebral ischemia, arterial and venous adverse events, and bleeding events are not known, we performed a meta-analysis of published RCTs of patients treated with or without bevacizumab in addition to standard chemotherapy. It is hoped that this meta-analysis will support the development of onco-cardiological follow-up and treatment strategies for these patients beyond the currently available standard oncologic care.

Methods

This meta-analysis was performed in accordance with the Preferred Reporting of Items for Systematic Meta-Analysis guidelines and the *Cochrane Handbook for Systematic Reviews of Interventions*.[25,26] The study was registered with PROSPERO (CRD42016054305).

Sources of Information and Search Strategies

A systematic search of studies published until November 21, 2016, was conducted using the MEDLINE, Cochrane, EMBASE, and Web of Science databases. We made our search specific and sensitive using MeSH terms and free text and considered studies in any language (Table S1).

Only those studies that complied with inclusion criteria as listed below were included:

1. Prospective RCTs involving patients with cancer.
2. Random assignment of patients to 2 groups: a bevacizumab group that included patients treated with bevacizumab along with standard chemotherapy and a control group that included patients treated with the same chemotherapy regimen without bevacizumab.
3. Reporting at least arterial and/or venous adverse events.
4. Sample size >100 patients.

The exclusion criteria were as follows:

1. Abstracts, reviews, animal studies, meta-analyses, and case reports.
2. Studies with single-arm bevacizumab treatment, treatment with bevacizumab in both groups described in the inclusion criteria, or treatment with other VEGF inhibitor.
3. Studies that did not report the selected outcomes or studies that reported the total (combined) number of events.
4. Subgroup population studies.
5. Radiotherapy.

After removing duplicates, R.I.M. and M.T. independently reviewed the abstracts. Any differences in results between the 2 investigators were resolved by discussion with T.R. When inclusion criteria appeared to be met, the entire text was reviewed. At the end of the review process, the full texts of the studies considered eligible were reviewed by all investigators.

Data Extraction and Quality Assessment

Two authors (R.I.M. and M.T.) independently performed the data extraction using a standard data extraction form that contained the following fields: publication details (name of the first author and year of publication); study design; characteristics of the study population (sample size, age, and sex distribution); type of cancer; chemotherapy regimen; dose of bevacizumab; mean follow-up; and study end points.

The trial quality was assessed according to the *Cochrane Handbook for Systematic Reviews of Interventions*.[25] Each study was assessed separately for the following biases: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data; (6) selective reporting (reporting bias); and (7) other bias.

Study End Points

The study end points were arterial adverse events, with a focus on cardiac and cerebral ischemia, venous adverse events, risk of bleeding, and arterial hypertension. The end points were defined according to the National Cancer Institute's common terminology criteria for adverse events.[27,28] Arterial adverse events were defined as one of the following: myocardial ischemia or infarction, cerebral infarction, cerebrovascular accident, cerebral ischemia, ischemic stroke, and peripheral or visceral arterial thrombotic events. Cardiac ischemia was defined as stable angina, unstable angina, non–ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction. Cerebral ischemia was defined as follows: asymptomatic, radiographic findings only or a transient ischemic event with neurological deficit shorter than 24 hours or a cerebral vascular accident with neurological deficit longer than 24 hours. Venous adverse events were defined as one of the following: deep vein thrombosis, pulmonary embolism, and mesenteric or any other vein thrombosis. Bleeding was defined as any type of bleeding. Arterial hypertension was defined as a new occurrence of arterial tension values >140/90 mm Hg.

Statistical Analysis

The meta-analysis was conducted on eligible studies by dividing the patients into the following 2 groups: the bevacizumab group, which included patients with cancer treated with bevacizumab and standard chemotherapy regimens, and the control group, which included patients with cancer treated with standard chemotherapy without bevacizumab. The proportion of patients with adverse events receiving bevacizumab was compared with that of the control group in the same RCT. The data are expressed as the risk ratios (RRs) and 95% CIs for dichotomous outcomes.[29] For the analysis, we used both fixed-effects and random-effects models. We performed a subgroup analysis of each type of cancer, and we explored the relationship between the bevacizumab dose and adverse events by separating bevacizumab treatments into low-dose treatments (5 or 7.5 mg/kg per dose per schedule, which is equivalent to 2.5 mg/kg per week) and high-dose treatments (10 or 15 mg/kg per dose per schedule, which is equivalent to 5 mg/kg per week). Heterogeneity between studies was assessed using the Q statistic, and inconsistencies were quantified using the I^2 statistic. Because this test has poor power when there are few studies, we considered both the presence of significant heterogeneity at the 10% level of significance and a value of $I^2 \geq 56\%$ as an indicator of significant heterogeneity.[30] The presence of publication bias was assessed using the funnel plot test (Egger test). Studies with high precision are plotted near the average and studies with low precision are spread evenly on both sides of the average, creating a roughly funnel-shaped distribution. Deviation from this shape indicates publication bias.[31] Use of the funnel plot test was not recommended when the analysis included <10 studies.[25] All analyses were conducted using Review Manager version 5.3 (Revman, The Cochrane Collaboration).

Results

Study Selection

The study selection process is shown in Figure 1 as a Preferred Reporting of Items for Systematic Meta-Analysis flowchart. A total of 1450 full-text articles were assessed for eligibility and 22 studies were selected for the meta-

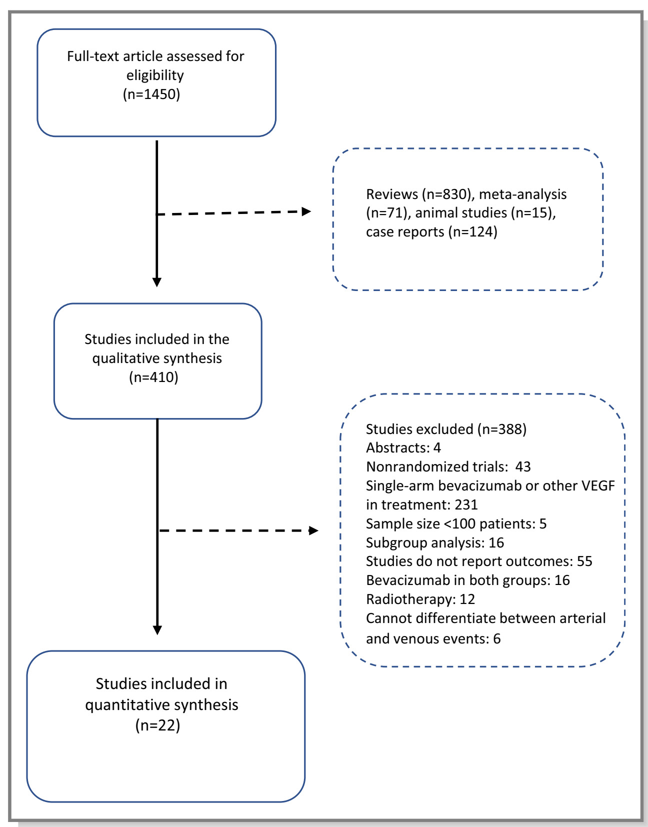


Figure 1. The Preferred Reporting of Items for Systematic Meta-Analysis flowchart. VEGF indicates vascular endothelial growth factor

Table 1. Studies Included in the Meta-Analysis

Study	Year	Type	Cancer Type	Treatment	Bevacizumab Dose, mg/kg per week	Mean Follow-Up, mo	No. of Patients
Allegra[32]	2009	RCT III	Stage II or III colon cancer	Bevacizumab+FOLFOX6 vs FOLFOX6	2.5	12	2647
Bennouna[33]	2013	RCT III	Metastatic colorectal cancer	Bevacizumab+oxaliplatin- or irinotecan-based chemotherapy vs chemotherapy	2.5	11	810
Cameron[34]	2013	RCT III	Triple-negative breast cancer	Bevacizumab+chemotherapy (anthracycline, taxane, or both) vs chemotherapy	5	32	2559
de Gramont[35]	2012	RCT III	Colon cancer	Bevacizumab+FOLFOX4 vs FOLFOX4	2.5	48	2271
Escudier[36]	2007	RCT III	Metastatic renal cell carcinoma	Bevacizumab+ interferon α-2a vs placebo+interferon α-2a	5	13	641
Gianni[37]	2013	RCT III	HER2-positive locally recurrent/metastatic breast cancer	Bevacizumab+docetaxel+trastuzumab vs docetaxel+trastuzumab	5	26	421
Giantonio[38]	2007	RCT III	Metastatic colorectal cancer	Bevacizumab+FOLFOX4 vs placebo+FOLFOX 4	5	28	572
Guan[39]	2011	RCT III	Metastatic colorectal cancer	Bevacizumab+mIFL vs mIFL	2.5	22	203
Hurwitz[40]	2004	RCT III	Metastatic colorectal cancer	Bevacizumab+IFL vs placebo+IFL	2.5	21	790
Hurwitz[41]	2005	RCT III	Metastatic colorectal cancer	Bevacizumab+fluoruracil+leucovirin vs placebo+IFL	2.5	30	207
Kabbinavar[42]	2003	RCT II	Metastatic colorectal cancer	Bevacizumab+fluorouracil and leucovorin vs placebo+fluorouracil and leucovorin	2.5 or 5	21	102
Kelly[43]	2012	RCT III	Metastatic castration-resistant prostate cancer	Bevacizumab+docetaxel+prednisone vs docetaxel+prednisone	5	23	1050
Miles[44]	2010	RCT III	Human epidermal growth factor receptor 2–negative metastatic breast cancer	Bevacizumab+docetaxel vs placebo+ docetaxel	2.5 or 5	25	730
Miller[45]	2007	RCT III	Metastatic breast cancer	Bevacizumab+paclitaxel vs paclitaxel	5	27	711
Niho[46]	2012	RCT II	Nonsquamous non–small cell lung cancer	Bevacizumab+carboplatin+paclitaxel vs carboplatin+paclitaxel	5	23	175
Ohtsu[47]	2011	RCT III	Advanced gastric cancer	Bevacizumab+cisplatin vs placebo+cisplatin	2.5	12	767
Perren[48]	2011	RCT III	Ovarian cancer	Bevacizumab+carboplatin+paclitaxel vs carboplatin+paclitaxel	2.5	42	1498
Pujade-Lauraine[49]	2014	RCT III	Platinum-resistant recurrent ovarian cancer	Bevacizumab+chemotherapy (pegylated liposomal doxorubicin, paclitaxel, or topotecan) vs chemotherapy	5	14	360
Reck[50]	2009	RCT III	Nonsquamous non–small cell lung cancer	Bevacizumab+cisplatin+gemcitabine vs cisplatin+gemcitabine	2.5 or 5	13	986
Rini[51]	2010	RCT III	Metastatic renal cell carcinoma	Bevacizumab+ interferon α-2a vs placebo+interferon α-2a	5	46	709
Saltz[52]	2008	RCT III	Metastatic colorectal cancer	Bevacizumab+FOLFOX4 or XELOX vs placebo+FOLFOX4 or XELOX	2.5	28	1369
Tebbutt[53]	2010	RCT III	Metastatic colorectal cancer	Bevacizumab+capecitabine vs capecitabine	2.5	31	472

FOLFOX, fluorouracil+folinate+oxaliplatin; IFL, irinotecan+leucovorin+fluorouracil; mIFL, modified irinotecan+leucovorin+fluorouracil; RCT, randomized controlled trial; XELOX, capecitabine+oxaliplatin.

analysis.[32–53] The characteristics of the selected studies are shown in Table 1. The quality of the included studies was high, as analyzed according to the recommendations of the Cochrane handbook (Figure S1).[25] Ten studies[32,33,35,38–43,52,53] included 9443 patients (47.09% of all patients) with colorectal cancer, 4 studies[19,34,37,45] included 4421 patients (22.04% of all patients) with breast cancer, 2 studies[48,49] included 1858 patients (9.26% of all patients) with ovarian cancer, 2 studies[36,51] included 1350 patients (6.73% of all patients) with renal cell cancer, 2 studies[46,50] included 1161 patients (5.79% of all patients) with non–small lung cell cancer, 1 study[43] included 1050 patients (5.23% of all patients) with prostate cancer, and 1 study[47] included 767 patients (3.82% of all patients) with gastric cancer. Eleven studies were included in the low-dose group[32–35,39–41,47,48,52,53] (2.5 mg/kg per week), 7 studies were included in the high-dose (5 mg/kg per week) group,[36,37,43,45,46,49,51] and 3 studies[42,44,50] had patients treated with both regimens that could be separated.

Bevacizumab and Arterial Adverse Events

The patients treated with bevacizumab were at a higher risk of arterial adverse events compared with controls (RR, 1.37; 95% CI, 1.10–1.70 [P=0.004]). This result was obtained by pooling the data from 19 randomized studies[32–41,44–53] including 18 028 patients (Figure 2). The heterogeneity between the included studies was not significant. The risk of bias for reporting arterial adverse events was low based on the funnel plot test (Figure S2). The risk for arterial adverse events was higher in the high-dose bevacizumab group (RR, 1.71; 95% CI, 1.06–2.77 [P=0.03]), as reported from 9 studies[34,36–38,45,46,49–51] including 6671 patients, without significant heterogeneity. The risk for arterial adverse events was not significantly increased in the low-dose bevacizumab group (RR, 1.22; 95% CI, 0.97–1.54 [P=0.09]). The analysis included 12 015 patients from 12 studies.* Arterial adverse events were defined as one of myocardial ischemia or infarction, cerebral infarction, cerebrovascular accident, cerebral ischemia, ischemic stroke, and peripheral or visceral arterial thrombotic events, as defined by the National Cancer Institute's Common Toxicity Criteria.[27,28] To provide a more specific description of the subtypes of arterial events, we extracted from our data the RRs for cardiac and cerebral ischemic adverse events. Cardiac ischemia was defined as stable angina, unstable angina, non–ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction. Cerebral ischemia was defined as asymptomatic, radiographic findings only or a transient ischemic event with neurological deficit shorter than 24 hours or a cerebral vascular accident with neurological deficit longer than 24 hours.

Bevacizumab and cardiac ischemia

The patients treated with bevacizumab were at higher risk of cardiac ischemia compared with the controls (RR, 2.47; 95% CI, 1.4–4.36 [P=0.002]). This result was obtained by pooling the data extracted from 5 studies[32,33,38,43,51] that reported outcomes for a total of 5828 patients (Figure 3A). A total of 3457 patients had colorectal cancer, 1050 had prostate cancer, 709 had renal cancer, and 572 had breast cancer. The heterogeneity between the selected studies was not significant.

When pooling data from high-dose bevacizumab from 3 studies[38,43,51] that reported on cardiac ischemia, with a total number of 2371 patients, the RR was nearly doubled compared with that obtained by pooling data from all the patients taking bevacizumab, with a value of 4.4 (95% CI, 1.59–12.17; P=0.004), with statistically insignificant heterogeneity (Figure 3B). The low-dose bevacizumab analysis included 3457 patients from 2 studies,[32,33] with an RR of 1.76 (95% CI, 0.86–3.59; P=0.12).

Bevacizumab and cerebral ischemia

An RR of 3.11 (95% CI, 1.46–6.65; P=0.003) indicated a higher risk of cerebral ischemia for patients treated with bevacizumab versus controls. The outcome was reported in 6 studies[32,38,42,43,45,51] for a total number of 5791 patients (Figure 3C). A total of 3321 patients had colorectal cancer, 1050 had prostate cancer, 711 had breast cancer, and 709 had renal cancer. The heterogeneity between the selected studies was statistically insignificant.

When pooling data from high-dose bevacizumab from 5 studies[19,38,42,43,54] that reported on cerebral ischemia, with a total of 3109 patients, the RR was 2-fold higher than that obtained by pooling data from all the patients taking bevacizumab, with a value of 6.69 (95% CI, 2.17–20.66; P=0.001) and not significant heterogeneity (Figure 3D). The low-dose bevacizumab analysis included 2717 patients from 2 studies,[32,42] with an RR for cerebral ischemia of 0.84 (95% CI, 0.27–2.63; P=0.77).

Bevacizumab and Venous Adverse Events

The patients treated with bevacizumab were at higher risk of venous adverse events compared with controls (RR, 1.29; 95% CI, 1.13–1.48 [P<0.001]). The result was obtained by pooling the data from 18 studies,[32–37,40–42,44–50,52,53] including a total of 17 339 patients (Figure 4). The heterogeneity was statistically insignificant among the studies. The risk of bias for reporting the venous adverse events was low (Figure S3). The analysis of high-dose bevacizumab included 6068 patients from 9 studies[34,36,37,42,44–46,49,50] and yielded an RR of 1.08 (95% CI, 0.79–1.47; P=0.63). The analysis of low-dose bevacizumab included 11 564 patients from 12 studies† and generated an RR of 1.36 (95% CI, 1.17–1.59; P<0.0001).

*32, 33, 35, 39–41, 44, 47, 48, 50, 52, 53.

†32, 33, 35, 40–42, 44, 47, 48, 50, 52, 53.

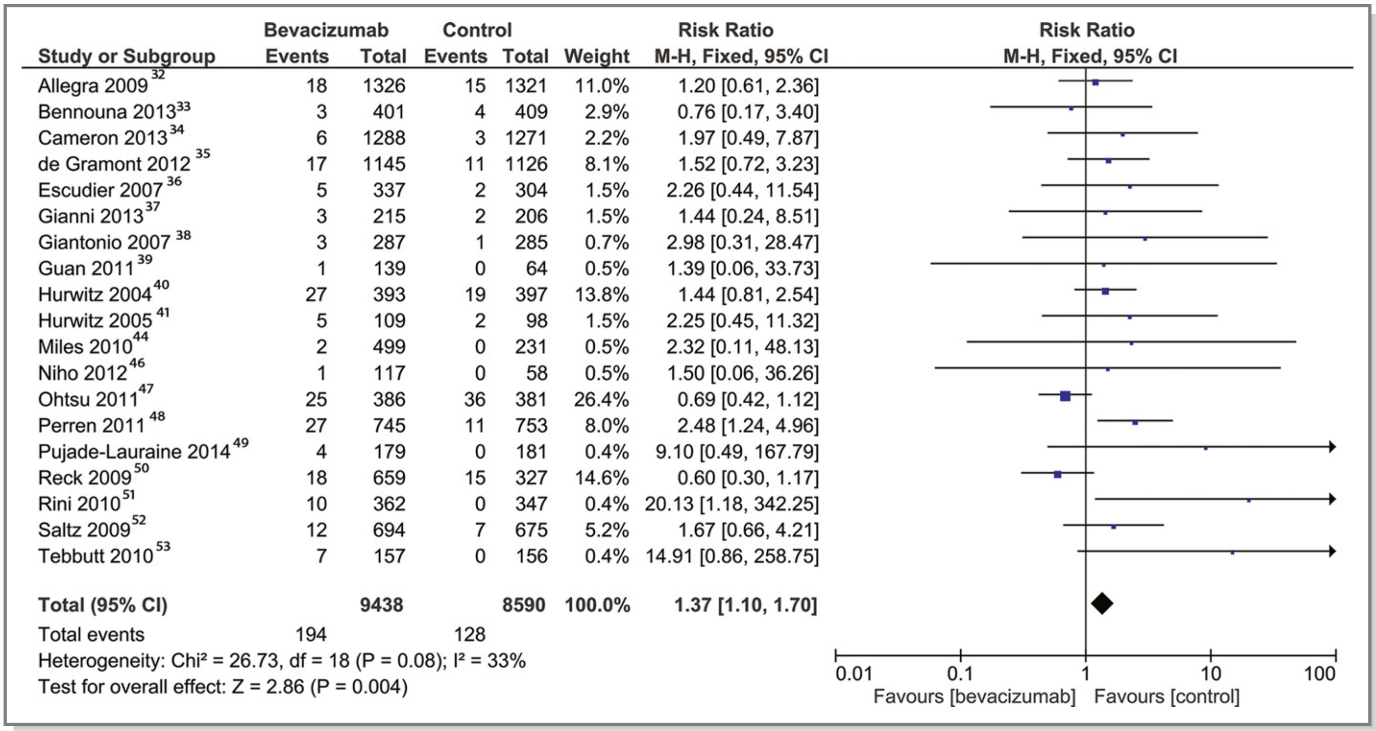


Figure 2. Overall estimate and estimates from each study of the risk ratio (RR) of arterial adverse events associated with bevacizumab treatment. The first author and the publication year were used for each study. The total number of events and the sample size are shown for each study. The weight of each study in the final analysis is indicated as a percentage. The RR for each study is shown numerically on the left and graphically on the right. Square boxes denote the risk ratio, horizontal lines represent 95% CIs, and the diamond plot represents the overall results of the included trials. Weights are from a fixed-effects analysis. M-H indicates Mantel-Haenszel statistical method.

Bevacizumab and Bleeding

The risk of bleeding was higher in the bevacizumab group (RR, 2.74; 95% CI, 2.38–3.15 [$P<0.001$]) (Figure 5A). The analysis included 19 studies[32,33,35–39,41,42,44–53] consisting of 16 701 patients. The heterogeneity between the studies was significant and the risk of bias was low (Figure 5B).

The risk of bleeding was higher in the high-dose bevacizumab group (RR, 3.32; 95% CI, 2.61–4.22 [$P<0.001$]); this analysis was based on data pooled from 10 studies[36–38,42,44–46,49–51] of a total of 4790 patients. The RR of bleeding between groups was 2.98 (95% CI, 2.47–3.61 [$P<0.00001$]), when the data were pooled from 12 studies of low-dose bevacizumab with 11 295 patients.[‡]

Bevacizumab and Arterial Hypertension

The risk of arterial hypertension was higher in the bevacizumab group (RR, 4.73; 95% CI, 4.15–5.39 [$P<0.001$]) (Figure 6A). The heterogeneity between studies was statistically significant. The risk of bias was low (Figure 6B). The risk for arterial hypertension was higher in the high-dose bevacizumab group (RR, 7.11; 95% CI, 5.6–9.03 [$P<0.001$]), and it remained high in the low-dose bevacizumab group with an RR of 5.07 (95% CI, 4.26–6.03 [$P<0.00001$]).

Heterogeneity Between Studies, Inconsistency, and Publication Bias

There was no significant heterogeneity between studies, except for the bleeding and arterial hypertension analyses, as previously decribed (Figures 5A and 6A). The publication bias was not significant, as assessed using the Egger test.

Sensitivity Analysis

A sensitivity analysis was performed by excluding each study, in turn, from the analysis to address the relative importance of each study. Bevacizumab treatment remained a risk factor for the selected outcomes.

Subgroup Analysis

There was no significant difference in the age of the patients with different subtypes of cancer. The mean patient age in the bevacizumab group was 58±4 years compared with

[‡]32, 33, 35, 39, 41, 42, 44, 47, 48, 50, 52, 53.

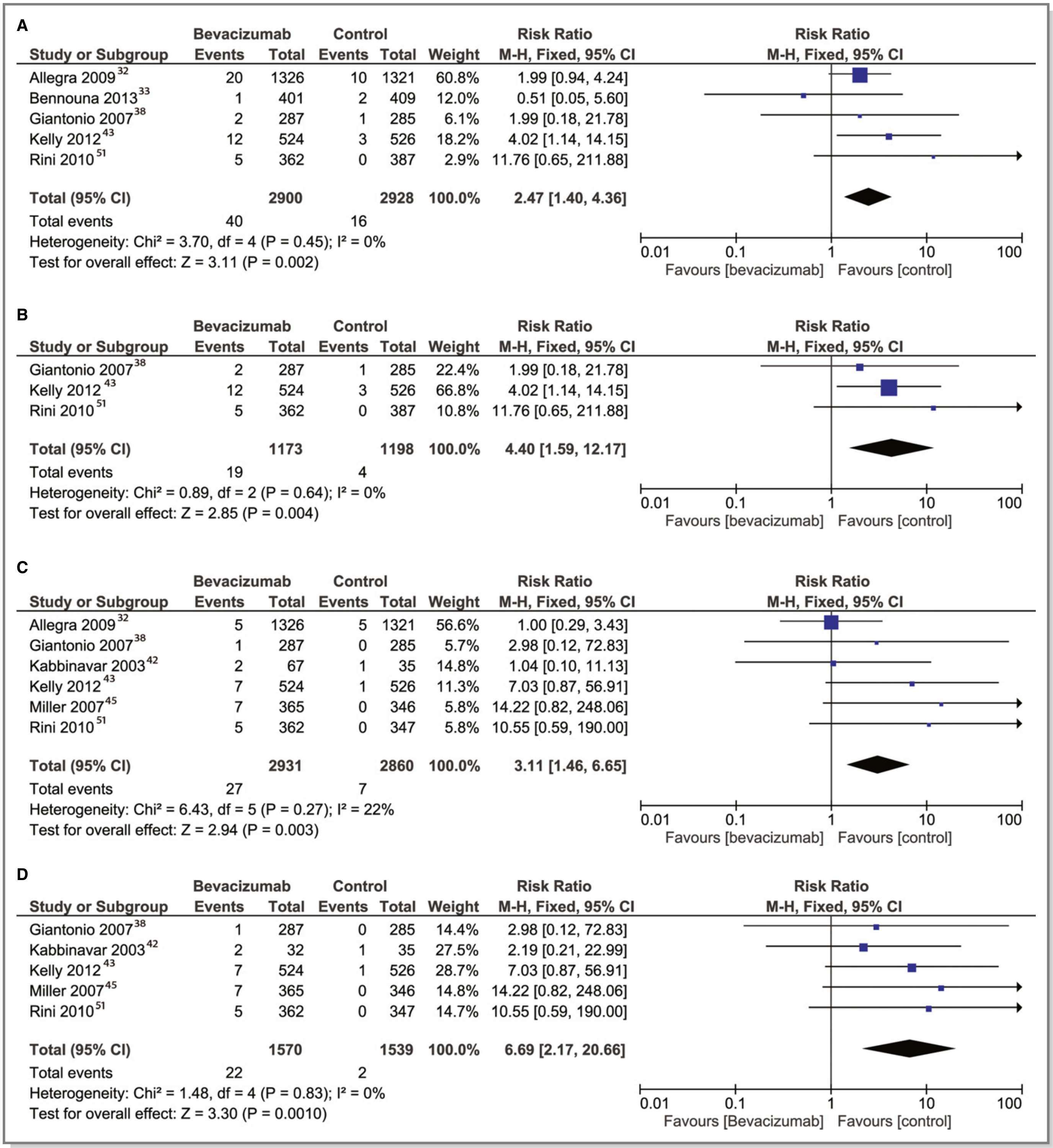


Figure 3. Overall estimate and estimates from each study of the risk ratio (RR) of cardiac ischemia associated with bevacizumab treatment (A), cardiac ischemia associated with high-dose bevacizumab treatment (B), cerebral ischemia associated with bevacizumab treatment (C), and cerebral ischemia associated with a high-dose bevacizumab regimen (D). The first author and the publication year were used for each study. The total number of events and sample size are shown for each study. The weight of each study in the final analysis is shown in percentages. The RR for each study is shown numerically on the left and graphically on the right. Square boxes denote the RR, horizontal lines represent 95% CIs, and the diamond plot represents overall results of the included trials. Weights are from fixed-effects analysis. M-H indicates Mantel-Haenszel statistical method.

Study or Subgroup	Bevacizumab Events	Bevacizumab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Allegra 2009[32]	83	1326	60	1321	16.5%	1.38 [1.00, 1.90]
Bennouna 2013[33]	19	401	12	409	3.3%	1.61 [0.79, 3.28]
Cameron 2013[34]	22	1288	19	1271	5.2%	1.14 [0.62, 2.10]
de Gramont 2012[35]	94	1145	63	1126	17.4%	1.47 [1.08, 2.00]
Escudier 2007[36]	10	337	3	304	0.9%	3.01 [0.84, 10.82]
Gianni 2013[37]	4	215	6	206	1.7%	0.64 [0.18, 2.23]
Hurwitz 2004[40]	49	393	45	397	12.3%	1.10 [0.75, 1.61]
Hurwitz 2005[41]	10	109	11	98	3.2%	0.82 [0.36, 1.84]
Kabbinavar 2003[42]	10	67	2	35	0.7%	2.61 [0.61, 11.27]
Miles 2010[44]	7	499	7	231	2.6%	0.46 [0.16, 1.30]
Miller 2007[45]	9	365	5	346	1.4%	1.71 [0.58, 5.04]
Niho 2012[46]	5	117	2	58	0.7%	1.24 [0.25, 6.20]
Ohtsu 2011[47]	5	386	8	381	2.2%	0.62 [0.20, 1.87]
Perren 2011[48]	50	745	31	735	8.5%	1.59 [1.03, 2.46]
Pujade-Lauraine 2014[49]	5	179	8	181	2.2%	0.63 [0.21, 1.89]
Reck 2009[50]	47	659	21	327	7.7%	1.11 [0.68, 1.83]
Saltz 2009[52]	54	694	33	675	9.2%	1.59 [1.05, 2.42]
Tebbutt 2010[53]	16	157	16	156	4.4%	0.99 [0.52, 1.92]
Total (95% CI)		**9082**		**8257**	**100.0%**	**1.29 [1.13, 1.48]**
Total events	499		352			

Heterogeneity: Chi² = 17.20, df = 17 (P = 0.44); I² = 1%
Test for overall effect: Z = 3.82 (P = 0.0001)

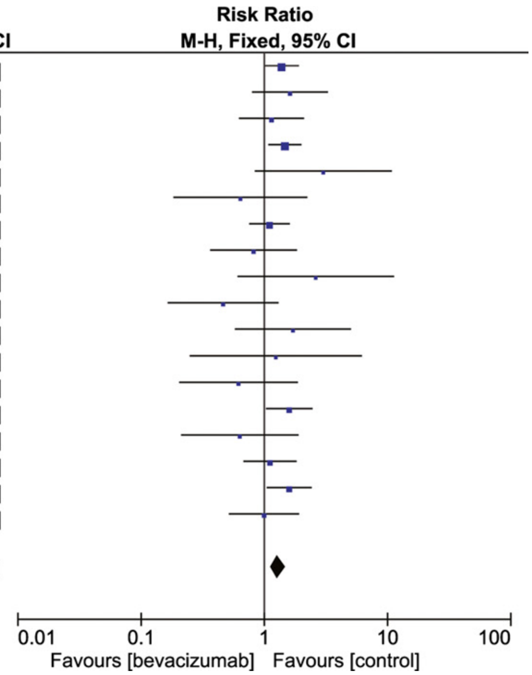


Figure 4. Overall estimate and estimates from each study of the risk ratio (RR) of venous adverse events associated with bevacizumab treatment. The first author and the publication year were used for each study. The total number of events and the sample size are shown for each study. The weight of each study in the final analysis is indicated as a percentage. The RR for each study is shown numerically on the left and graphically on the right. Square boxes denote the RR, horizontal lines represent 95% CIs, and the diamond plot represents the overall results of the included trials. Weights are from a fixed-effects analysis.

58±4 years in the control group (P=0.9). The sex distribution was not different between the bevacizumab group and the control group. Taken together, based on the present data, the influence of sex and age on bevacizumab-induced cardiovascular events cannot be determined.

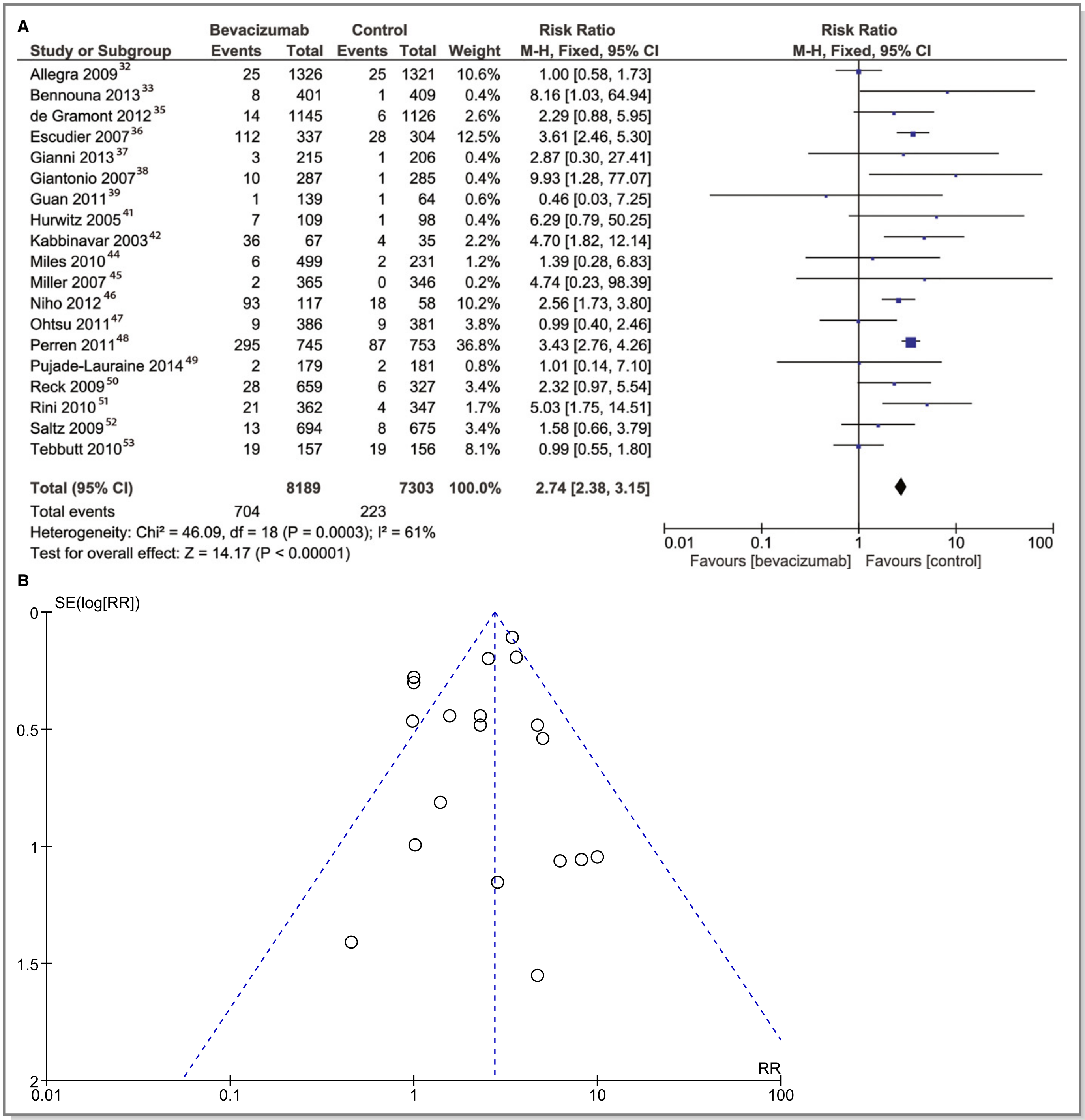
Bevacizumab increased the risk of arterial adverse events in colorectal, renal, and ovarian cancer, with the highest RR observed for renal cancer, and increased the risk of cardiac ischemia in prostate cancer. The risk of venous adverse events was increased in colorectal cancer. For the other types of cancer, the risk of arterial and venous adverse events was similar between groups. The risk of bleeding was increased in colorectal, renal, ovarian, and lung cancer, with the highest RR for renal cancer. The risk of arterial hypertension was increased in all types of cancer, with the highest RR for breast cancer (Table 2).

We performed a subgroup analysis considering the follow-up time of each study. We divided the studies into studies with 11 to 14 months of follow-up,[32,33,36,47,49,50] 21 to 24 months of follow-up,[37,39,40,42,43,46] and more than 24 months of follow-up.[§] The RR for arterial adverse events, cerebral ischemia, and venous adverse events was significantly higher for the group with more than 24 months of follow-up, without reaching significance for shorter follow-up times. Cardiac ischemia was significantly higher for the group with 21 to 24 months of follow-up, but this result was derived from a single study. Bleeding and arterial hypertension were significantly higher in the bevacizumab group for all 3 subgroups, irrespective of the follow-up times (Table 3).

Discussion

We performed a comprehensive meta-analysis of the cardiovascular complications in patients with cancer treated with bevacizumab compared with those treated with standard chemotherapy. The study pooled data from 22 studies, including more than 20 000 patients. The main findings are as follows: (1) patients treated with bevacizumab have a significantly higher risk of developing arterial adverse events compared with controls, with a higher risk of cardiac and cerebral ischemia; (2) patients treated with bevacizumab have a higher risk of venous adverse events compared with controls; (3) the risk of bleeding is significantly higher in patients with cancer treated with bevacizumab compared with controls; (4) the risk of developing arterial hypertension is significantly higher in the bevacizumab group; (5) patients

[§]34, 35, 38, 41, 44, 45, 48, 51–53.

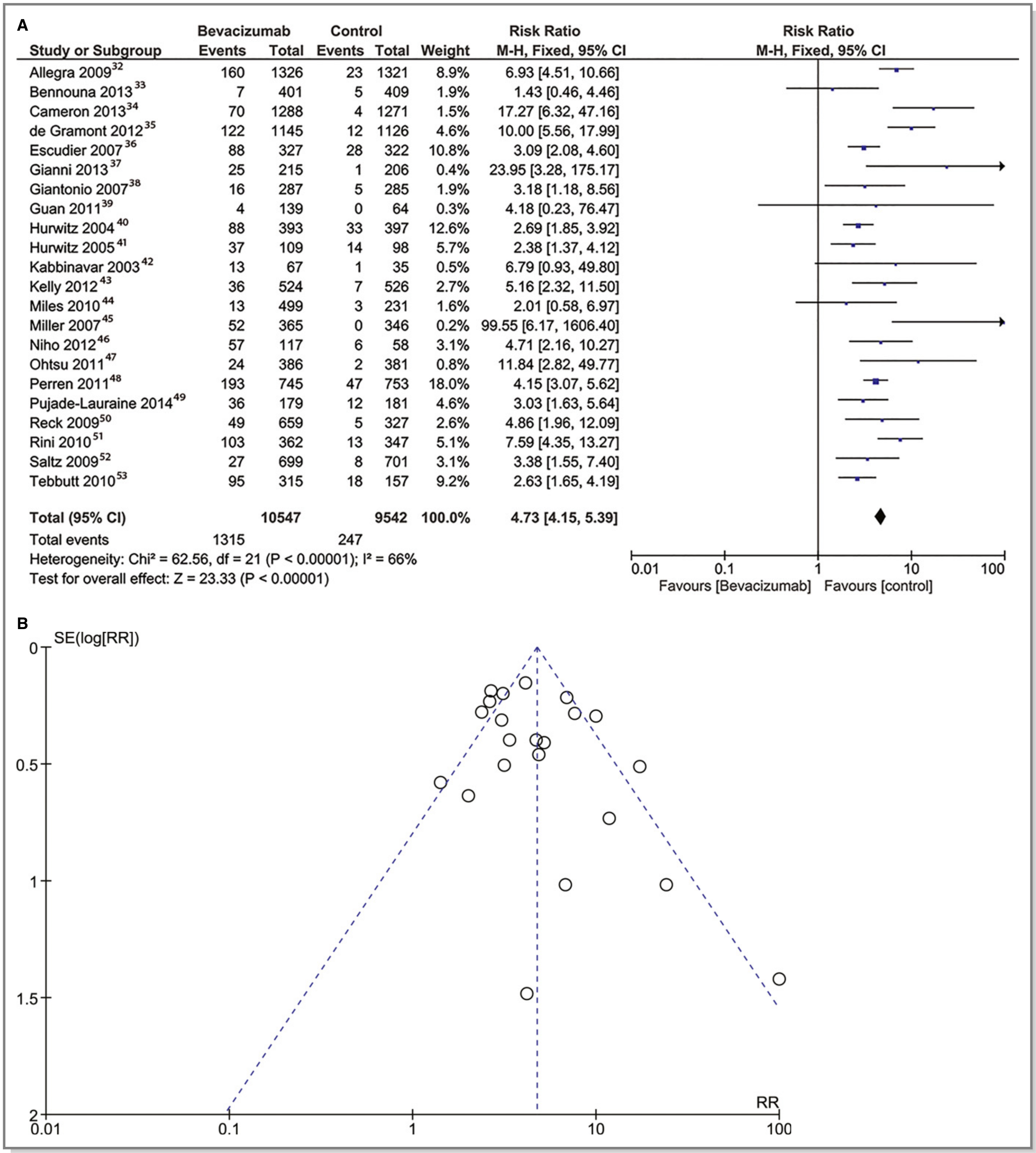


Study or Subgroup	Bevacizumab Events	Bevacizumab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Allegra 2009[32]	25	1326	25	1321	10.6%	1.00 [0.58, 1.73]
Bennouna 2013[33]	8	401	1	409	0.4%	8.16 [1.03, 64.94]
de Gramont 2012[35]	14	1145	6	1126	2.6%	2.29 [0.88, 5.95]
Escudier 2007[36]	112	337	28	304	12.5%	3.61 [2.46, 5.30]
Gianni 2013[37]	3	215	1	206	0.4%	2.87 [0.30, 27.41]
Giantonio 2007[38]	10	287	1	285	0.4%	9.93 [1.28, 77.07]
Guan 2011[39]	1	139	1	64	0.6%	0.46 [0.03, 7.25]
Hurwitz 2005[41]	7	109	1	98	0.4%	6.29 [0.79, 50.25]
Kabbinavar 2003[42]	36	67	4	35	2.2%	4.70 [1.82, 12.14]
Miles 2010[44]	6	499	2	231	1.2%	1.39 [0.28, 6.83]
Miller 2007[45]	2	365	0	346	0.2%	4.74 [0.23, 98.39]
Niho 2012[46]	93	117	18	58	10.2%	2.56 [1.73, 3.80]
Ohtsu 2011[47]	9	386	9	381	3.8%	0.99 [0.40, 2.46]
Perren 2011[48]	295	745	87	753	36.8%	3.43 [2.76, 4.26]
Pujade-Lauraine 2014[49]	2	179	2	181	0.8%	1.01 [0.14, 7.10]
Reck 2009[50]	28	659	6	327	3.4%	2.32 [0.97, 5.54]
Rini 2010[51]	21	362	4	347	1.7%	5.03 [1.75, 14.51]
Saltz 2009[52]	13	694	8	675	3.4%	1.58 [0.66, 3.79]
Tebbutt 2010[53]	19	157	19	156	8.1%	0.99 [0.55, 1.80]
Total (95% CI)		**8189**		**7303**	**100.0%**	**2.74 [2.38, 3.15]**
Total events	704		223			

Heterogeneity: Chi² = 46.09, df = 18 (P = 0.0003); I² = 61%
Test for overall effect: Z = 14.17 (P < 0.00001)

Figure 5. Overall estimate and estimates from each study of the risk ratio (RR) of bleeding (A) and risk of bias for bleeding (B) associated with bevacizumab treatment. The first author and the publication year were used for each study. The total number of events and the sample size are shown for each study. The weight of each study in the final analysis is indicated as a percentage. The relative risk for each study is shown numerically on the left and graphically on the right. Square boxes denote the RR, horizontal lines represent 95% CIs, and the diamond plot represents the overall results of the included trials. Weights are from a fixed-effects analysis. Each dot represents one study included in the analysis of bleeding events. The SE (log RR) axis represents study precision, and the risk ratio (RR) axis shows the study results. M-H indicates Mantel-Haenszel statistical test.

treated with high-dose bevacizumab have a higher risk of arterial adverse events, cardiac and cerebral ischemia, bleeding, and arterial hypertension, but the dosage had no effect on venous adverse events; and (6) the highest RR of arterial adverse events was observed for renal cancer, the highest RR of cardiac ischemia for prostate cancer, the higher



Study or Subgroup	Bevacizumab Events	Bevacizumab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Allegra 2009[32]	160	1326	23	1321	8.9%	6.93 [4.51, 10.66]
Bennouna 2013[33]	7	401	5	409	1.9%	1.43 [0.46, 4.46]
Cameron 2013[34]	70	1288	4	1271	1.5%	17.27 [6.32, 47.16]
de Gramont 2012[35]	122	1145	12	1126	4.6%	10.00 [5.56, 17.99]
Escudier 2007[36]	88	327	28	322	10.8%	3.09 [2.08, 4.60]
Gianni 2013[37]	25	215	1	206	0.4%	23.95 [3.28, 175.17]
Giantonio 2007[38]	16	287	5	285	1.9%	3.18 [1.18, 8.56]
Guan 2011[39]	4	139	0	64	0.3%	4.18 [0.23, 76.47]
Hurwitz 2004[40]	88	393	33	397	12.6%	2.69 [1.85, 3.92]
Hurwitz 2005[41]	37	109	14	98	5.7%	2.38 [1.37, 4.12]
Kabbinavar 2003[42]	13	67	1	35	0.5%	6.79 [0.93, 49.80]
Kelly 2012[43]	36	524	7	526	2.7%	5.16 [2.32, 11.50]
Miles 2010[44]	13	499	3	231	1.6%	2.01 [0.58, 6.97]
Miller 2007[45]	52	365	0	346	0.2%	99.55 [6.17, 1606.40]
Niho 2012[46]	57	117	6	58	3.1%	4.71 [2.16, 10.27]
Ohtsu 2011[47]	24	386	2	381	0.8%	11.84 [2.82, 49.77]
Perren 2011[48]	193	745	47	753	18.0%	4.15 [3.07, 5.62]
Pujade-Lauraine 2014[49]	36	179	12	181	4.6%	3.03 [1.63, 5.64]
Reck 2009[50]	49	659	5	327	2.6%	4.86 [1.96, 12.09]
Rini 2010[51]	103	362	13	347	5.1%	7.59 [4.35, 13.27]
Saltz 2009[52]	27	699	8	701	3.1%	3.38 [1.55, 7.40]
Tebbutt 2010[53]	95	315	18	157	9.2%	2.63 [1.65, 4.19]
Total (95% CI)		**10547**		**9542**	**100.0%**	**4.73 [4.15, 5.39]**
Total events	1315		247			

Heterogeneity: Chi² = 62.56, df = 21 (P < 0.00001); I² = 66%
Test for overall effect: Z = 23.33 (P < 0.00001)

Figure 6. Overall estimate and estimates from each study of the risk ratio (RR) of arterial hypertension (A) and risk of bias for arterial hypertension (B) associated with bevacizumab treatment. The first author and the publication year were used for each study. The total number of events and the sample size are shown for each study. The weight of each study in the final analysis is indicated as a percentage. The relative risk for each study is shown numerically on the left and graphically on the right. The square boxes denote the RR, horizontal lines represent 95% CIs, and the diamond plot represents the overall results of the included trials. Weights are from a fixed-effects analysis. Each dot represents one study included in the analysis of bleeding events. The SE (log risk ratio [RR]) axis represents study precision, and the RR axis shows the study results. M-H indicates Mantel-Haenszel statistical method.

Table 2. Risk ratios for Adverse Events for Each Type of Cancer

Cancer Type	Arterial Adverse Events	Cardiac Ischemia	Cerebral Ischemia	Venous Adverse Events	Bleeding	Arterial Hypertension
Colorectal cancer	1.54 (1.12–2.12), *P*=0.008*	1.77 (0.90–3.48), *P*=0.1	1.15 (0.41–3.20), *P*=0.79	1.34 (1.14–1.58), *P*=0.0003*	1.78 (1.32–2.38), *P*=0.0001*	3.68 (2.44–5.53), *P*<0.00001*
Renal cancer	5.75 (1.53–21.58), *P*=0.01*	11.76 (0.65–211.88), *P*=0.09	10.55 (0.59–190.00), *P*=0.11	3.01 (0.84–10.82), *P*=0.09	3.78 (2.63–5.43), *P*<0.00001*	4.74 (1.94–11.61), *P*=0.0006*
Breast cancer	1.82 (0.65–5.09), *P*=0.25	Not estimable	14.22 (0.82–248.06), *P*=0.07	0.94 (0.56–1.57), *P*=0.8	2.15 (0.67–6.88), *P*=0.2	13.45 (2.69–67.21), *P*=0.02*
Ovarian cancer	2.77 (1.42–5.40), *P*=0.003*	Not estimable	Not estimable	1.16 (0.49–2.74), *P*=0.74	3.37 (2.72–4.18), *P*<0.00001*	3.91 (2.98–5.13), *P*=0.00001*
Lung cancer	0.62 (0.32–1.20), *P*=0.16	Not estimable	Not estimable	1.12 (0.70–1.80), *P*=0.64	2.50 (1.73–3.60), *P*<0.00001*	4.77 (2.64–8.63), *P*<0.00001*
Cancer type	Arterial adverse events	Cardiac ischemia	Cerebral ischemia	Venous adverse events	Bleeding	Arterial hypertension
Prostate cancer	Not estimable	4.02 (1.14–14.15), *P*=0.03*	7.03 (0.87–56.91), *P*=0.07	Not estimable	Not estimable	5.16 (2.32–11.50), *P*<0.0001*
Gastric cancer	0.69 (0.42–1.12), *P*=0.13	Not estimable	Not estimable	0.62 (0.20–1.87), *P*=0.39	0.99 (0.40–2.46), *P*=0.98	11.84 (2.82–49.77), *P*=0.007*

Data are expressed as risk ratio (95% CI), *P* value.
*Statistically significant data.

RR of bleeding for renal cancer, and the highest RR of arterial hypertension for breast cancer. These findings are of substantial importance for the daily care of patients with cancer and could contribute to the advancement of treatment protocols, with emphasis on cardiovascular surveillance, prevention, and multidisciplinary decisions by cardio-oncology teams.

Bevacizumab is the pioneer of all VEGF monoclonal antibodies and it has been extensively used since its first approval more than 1 decade ago. Consequently, it is mandatory to characterize the entire range of its potentially adverse effects. Notably, the underlying mechanisms through which bevacizumab produces a prothrombotic status have not yet been fully elucidated. It is well-known that hypertension injures the endothelium, leading to a prothrombotic status.[55] This effect may be caused and exacerbated by bevacizumab-dependent inhibition of VEGF, leading to a decrease in NO generation by endothelial cells. NO, in turn, is a potent vasodilator whose absence contributes to platelet aggregation and adhesion.[56–59] Furthermore, VEGF blockade increases the expression of proinflammatory genes.[56] In addition, these effects could accelerate in situ thrombus formation and explain the higher incidence of arterial and venous adverse events, including cardiac and cerebral ischemia. Conversely, the use of bevacizumab was associated with an increased risk of bleeding explained by the inhibition of VEGF, which diminishes the regenerative capacity of endothelial cells and causes endothelial defects that expose procoagulant phospholipids on the luminal plasma membrane or underlying matrix, leading to both thrombosis and hemorrhage.[60–63]

Naturally, the majority of the current RCTs and meta-analyses in the scope of VEGF inhibition have focused on either overall survival rates or event-free survival, particularly in patients with colorectal cancer, without describing the complete range of adverse events in all types of malignancies for which bevacizumab is prescribed.[64–66]

A higher incidence of arterial adverse events in patients treated with bevacizumab has been previously described, concordant with our findings.[6,24,67,68] In contrast to prior analyses, here we have included several novel and important studies, assessed the differential impact of different cancer diagnoses on various types of arterial events, and approached the potential impact of dosage on risk. In addition, we have attempted to resolve contradictory reports on the risk of venous events, with respect to specific tumor types.[17,69,70] When reporting the venous adverse events in all cancer types, the results were divergent, with patients treated with bevacizumab exhibiting similar or higher risk of venous adverse events compared with controls for both low-dosage and high-dosage subgroups.[71,72] These outcomes are in contradiction with our findings, suggesting that this issue should be further addressed in future RCTs, in order to

Table 3. Risk ratios for Adverse Events for Different Follow-Up Times

Follow-Up Time	11–14 mo	21–24 mo	>24 mo
Arterial adverse events	0.86 (0.63–1.18), P=0.35	1.44 (0.85–2.44), P=0.18	2.40 (1.64–3.52), P<0.001*
Cardiac ischemia	1.75 (0.86–3.54), P=0.12	4.02 (1.14–14.15), P=0.03*	5.16 (0.91–29.33), P=0.06
Cerebral ischemia	1.00 (0.29–3.43), P=1	3.63 (0.85–15.45), P=0.08	12.39 (1.62–94.49), P=0.02*
Venous adverse events	1.26 (0.95–1.67), P=0.12	1.06 (0.74–1.51), P=0.75	1.37 (1.11–1.68), P=0.03*
Bleeding	2.26 (1.74–2.95), P<0.001*	2.84 (1.98–4.06), P<0.001*	2.96 (2.46–3.56), P<0.001*
Arterial hypertension	4.06 (2.52–6.54), P<0.001*	4.30 (2.59–7.14), P<0.001*	4.81 (3.10–7.46), P=0.001*

Data are expressed as risk ratio (95% CI), *P* value.
*Statistically significant.

precisely indicate the impact of tumor type, age, functional status, venous thromboembolism history, or the use of anticoagulants on developing venous adverse events.[72]

Cardiovascular adverse effects have been reported in colorectal cancer,[5,24,73–76] ovarian cancer,[17] non–small cell lung cancer,[70] breast cancer,[69] and renal cancer[77]; however, as previously mentioned, these analyses do not include information regarding the complete spectrum of cardiovascular adverse events, the type of events, the impact of the dosage, or the cancer type.[6,71] The incidence of adverse events was shown to differ based on cancer type, and this result is concordant with our findings.[78] Furthermore, the risk of arterial adverse events in different cancer subtypes is a controversial topic, with studies reporting an increased risk of arterial events in colorectal cancer and ovarian cancer,[17] but not non–small cell lung cancer[70] or breast cancer,[69] which is partially concordant with our results. We reported the highest risk of arterial adverse events for patients with renal cancer, which could be explained by the higher incidence of arterial hypertension in this cancerous disease, with its subsequent endothelial damage and thrombosis.[79] The different incidence of adverse events among specific cancer types could be partially explained by the variable expression of VEGF in different cancer types and subtypes.[80] Additional explanations of this effect could be the concurrent comorbidities, different stages of the carcinoma, the different effect of co-chemotherapies, and the lack of standardization in reporting the outcomes. Although we excluded patients who were treated with radiotherapy known to increase the risk of cardiovascular adverse events, the impact of chemotherapies such as 5-fluorouracil or taxanes cannot be dissociated from the global outcomes.[81] Taken together, randomized prospective studies are warranted regarding bevacizumab-associated cardiovascular events.

There is less evidence regarding dose-dependent increases in cardiovascular events. Here, we determined that higher-dose bevacizumab regimens are associated with an increased risk of arterial adverse events, including cardiac and cerebral ischemia, bleeding events, and arterial hypertension, with no effect on the occurrence of venous adverse events. Moreover, the low-dose regimens are not associated with a significantly higher incidence of arterial adverse effects, including cardiac and cerebral ischemia. These findings are similar to other analyses, but the small number of comparative studies, their small size, and the reporting modality make the comparison between dose regimens difficult.[78,82,83] The only prior study comparing low-dose and high-dose regimens showed no differences in terms of safety between the 2 regimens, but it should be noted that in that study patients were selected for second-line therapy, having been previously treated with bevacizumab, potentially limiting the generalizability of that result.[84] It would be of importance to establish the ideal bevacizumab dose that would have antitumoral effects without causing cardiovascular adverse events. In vitro studies have shown that lower doses are sufficient to induce vascular normalization and that higher doses are necessary to obtain a direct cytotoxic effect.[85] However, higher doses could generate additional unfavorable conditions, particularly hypoxia, that increase the incidence of adverse events.[86] As a consequence, the actual data do not have sufficient power to indicate the ideal bevacizumab dosage or an algorithm of dose reduction in patients with cancer at risk for cardiovascular disease.[19,50,82,83]

Bleeding events have been characterized as a major adverse event during therapy with bevacizumab. The risk of bleeding appears to be higher in patients treated with bevacizumab, concordant with our findings, but the risk of severe bleeding was not significantly increased in colorectal cancer.[60,61] The general risk of bleeding also includes minor bleeding events, such as epistaxis or gingival bleeding, and could be highly variable among subtypes of cancer, as shown in our report. In addition, the factors that increase the risk of hemorrhage could not be precisely identified, making the impact of bleeding on the management of these patients hard to estimate. The highest RR of bleeding in patients with renal cancer could be explained by the higher incidence of endothelial damage secondary to arterial hypertension.[79] The risk of bleeding is different among cancer types and depends on the stages of carcinoma, the presence of thrombocytopenia, renal and hepatic function, the presence of comorbidities, and predisposal to bleeding of each patient.[87] Further efforts are necessary to report indications that could be used as guidelines for clinical practice.[60]

The analysis of our data showed a low heterogeneity among studies for all outcomes, except for bleeding and arterial hypertension. In these 2 analyses, the heterogeneity could be explained by the fact that some studies report only high-grade bleeding and hypertension and not events of all grades.

Because of the paramount impact of severe cardiovascular adverse events on survival, the use of an integrative cardio-oncology approach has received increasing attention in the past years.[88] Until now, the strategies to prevent cardiovascular adverse events in patients with cancer treated with VEGF inhibitors, such as baseline cardiovascular risk assessment, optimal control of arterial hypertension, and adjustment of chemotherapy dosage, have received the main attention, while the preventive administration of low-molecular-weight heparin in these patients is controversial.[81,89] Routine thromboprophylaxy with low-molecular-weight heparin is not recommended for ambulatory patients with cancer, but it may be considered for selected high-risk patients. It is also indicated in the setting of major surgery and for the treatment of deep vein thrombosis or pulmonary embolism. The use of novel oral anticoagulants is not currently recommended for secondary prevention in patients with malignancy.[90] Data regarding the value of aspirin prophylaxis for arterial thromboembolism in patients treated with bevacizumab raises unsolved controversies about the benefit-risk balance.[24,91] The use of aspirin is limited at this moment to patients with multiple myeloma receiving antiangiogenesis agents with chemotherapy and/or dexamethasone, as an alternative to low-molecular-weight heparin.[92] In addition, the favorable cardiomyocyte protective role of statins that arise from the anthracycline-based studies could not be easily translated to antiangiogenic therapies because of different mechanisms of action and toxicity.[93,94] Moreover, the potential benefits of thromboprophylaxis would need to be carefully weighed against increased bleeding risk, and ideally in a prospective fashion in order to determine the optimal therapeutic attitude. As a consequence, there are still many unanswered questions regarding the efficacy of primary prevention or the effects of interrupting chemotherapy because of cardiovascular adverse events that need to be addressed in the future.[95,96] As derived from our subgroup analysis of the follow-up time, arterial and venous adverse events tend to be significant and proportionally higher with more than 24 months of follow-up, suggesting that these patients need long-term cardiological follow-up after treatment with bevacizumab.

Study Limitations

Our study has some limitations that need to be addressed. First, we analyzed different types of cancer treated with different chemotherapy regimens at different doses. Second, our study included all grades of adverse events, and some studies only reported high-grade events. Third, the population included in the selected studies could have been selected using strict exclusion criteria, and the included patients could have been at low risk of cardiovascular events. Finally, in most of the studies, the vascular adverse events were secondary end points and were not always reported accurately.

Conclusions

Treatment with bevacizumab increases the risk of arterial adverse events, particularly cardiac and cerebral ischemia, venous adverse events, bleeding, and arterial hypertension. This risk is additionally increased with high doses of bevacizumab. Further studies should determine the appropriate cardio-oncology management options.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table 1. The results of the search through Medline on the 21st November 2016

Nr of search	Query	Medline
1	bevacizumab and colorectal cancer	2726
2	VEGF and colorectal cancer	2524
3	bevacizumab and non-small cell lung cancer	941
4	bevacizumab and glioblastoma	780
5	bevacizumab and renal cell cancer	684
6	bevacizumab and cervical cancer	106
7	bevacizumab and ovarian cancer	575
8	angiogenesis inhibitors and colorectal neoplasms	3049
9	bevacizumab and colonic neoplasms	371
10	bevacizumab and rectal neoplasms	300
11	bevacizumab and thromboembolic events	293
12	bevacizumab and cardiac ischemia	44
13	bevacizumab and cerebral ischemia	33
14	bevacizumab and gastric cancer	151
Total		12577

Figure S1. The quality of the included studies as analysed per Cochrane Handbook's recommendation.

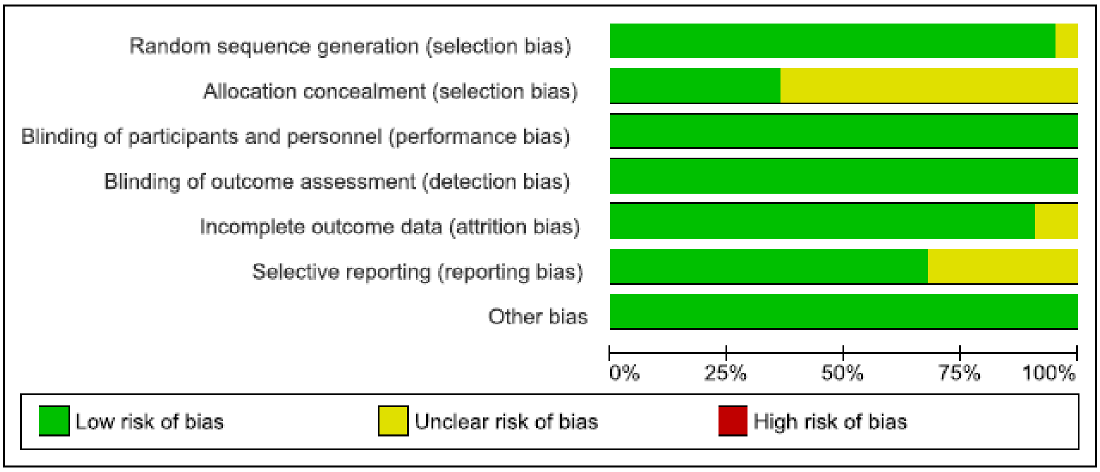
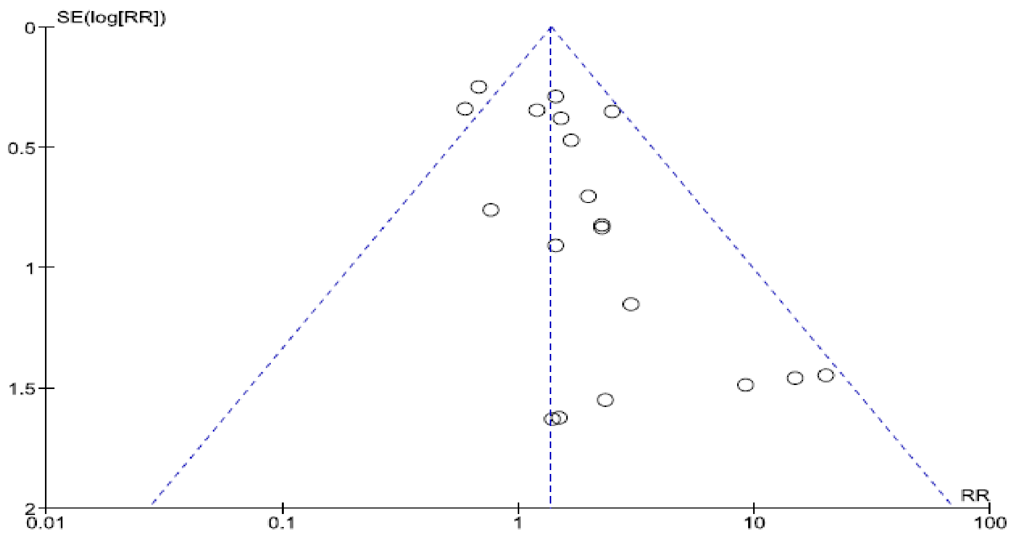
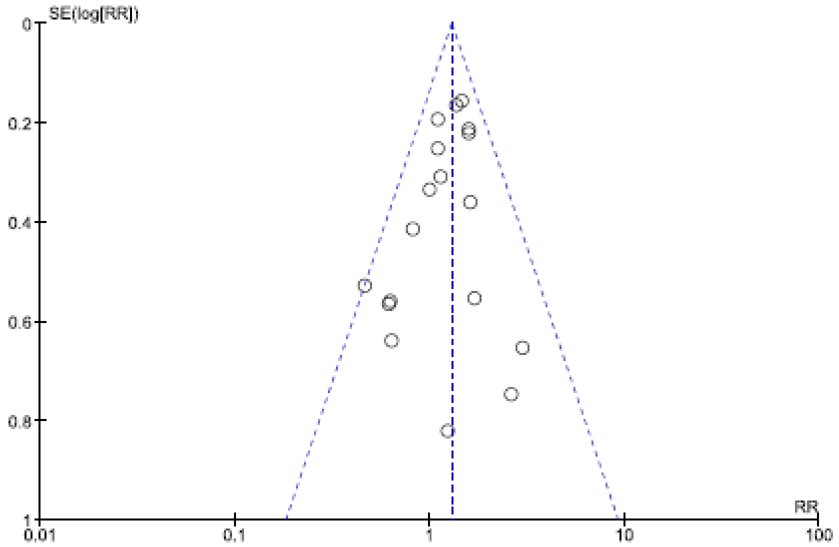


Figure S2. Risk of bias for arterial adverse events



Each dot represents one study included in the analysis of arterial adverse events. The SE (log RR) axis represents study precision, and the RR axis shows the study results.

Figure S3. Risk of bias for venous adverse events



Each dot represents one study included in the analysis of venous adverse events. The SE (log RR) axis represents study precision, and the RR axis shows the study results.