Risk of cardiac ischemia and arterial thromboembolic events with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis of randomized controlled trials

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CRD summary
The authors' cautious conclusions reflected the evidence presented, although poor reporting of review methods and study quality and an apparent lack of high-quality studies should be borne in mind.

Authors' objectives
To determine the impact of bevacizumab on the occurrence of arterial thromboembolic events in cancer patients.

Searching
PubMed was searched from 1966 to May 2009. Web of Science was searched. Abstracts presented at American Society of Clinical Oncology conferences between 2000 and May 2009 were searched. Search terms were reported. Reference lists of included studies and drug manufacturer submission documents were searched for additional articles.

Study selection
Prospective phase II or III randomised-controlled trials (RCTs) that directly compared bevacizumab with controls (placebo or best supportive care) in cancer patients who received concurrent therapy using a chemotherapeutic and/or biological agent were eligible for inclusion. Among a number of exclusion criteria, patients were excluded if they had significant cardiovascular or peripheral vascular disease, uncontrolled hypertension, serious non-healing wounds, pre-existing bleeding diatheses or brain metastasis. Also excluded were those who were taking non-steroidal anti-inflammatory drugs or had regular acetylsalicylic acid (aspirin) use that exceeded 325mg/day. Outcomes included events or incidence of arterial thrombosis (including cardiac ischaemia and stroke). Patients were required to have adequate hepatic, renal and haematologic function. Studies in which patients had certain conditions, such as significant cardiovascular disease, were excluded from the individual studies.

In the included studies, baseline Eastern Cooperative Oncology Group (ECOG) performance status was between 0 and 1 for most patients. Underlying malignancies comprised colorectal cancer (seven studies), non-small cell lung cancer (four studies), breast cancer (three studies), pancreatic cancer (two studies) renal cell cancer (three studies) and malignant mesothelioma (one study). Bevacizumab dose ranged from 2.5 to 5mg/kg/week. Concurrent treatments varied across studies (see paper for details).

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Study quality was assessed using previously published criteria based upon adequate blinding of randomisation, completeness of follow-up and objectivity of outcome measurements.

The authors did not state how many reviewers performed quality assessment.

Data extraction
Two reviewers independently extracted incidence (proportion) of patients with arterial thromboembolic events to calculate the relative risk (RR) for arterial thromboembolic events, and 95% confidence intervals (CI). Authors and drug manufacturers were contacted to clarify data queries. Discrepancies were resolved by consensus.

Methods of synthesis
Both fixed-effect and random-effects models were used to pool studies based on level of heterogeneity. Statistical heterogeneity was assessed using the Cochran Q test and $I^2$. To explore the impact of dose, bevacizumab dose was categorised as low (2.5mg/kg/week) or high (5mg/kg/week). Data were reported separately by underlying malignancy...
and tumour type. Arterial thromboembolic events were graded into all grades and high grades (grade 3 and above) according to National Cancer Institute common terminology criteria for adverse events (defined in the review). Publication bias was assessed using Begg and Egger tests.

Results of the review

Twenty RCTs (n=12,617 participants) were included in the review. Randomised treatment allocation sequences were generated in all trials. Six studies were double-blinded and placebo controlled. Five other trials used placebo as controls. Other trials had active controls. Median follow-up duration ranged from 6.7 to 28 months.

Compared with controls, patients treated with bevacizumab had a significantly increased risk of overall arterial thromboembolic events (RR 1.44, 95% CI 1.08 to 1.91; n=12,617) and high-grade cardiac ischaemia (RR 2.14, 95% CI 1.12 to 4.08; n=4,473), but did not significantly increase the risk of ischaemic stroke (n=4,541). There was no significant statistical heterogeneity for these comparisons. Subgroup analyses showed that there was a significantly increased risk for all-grade arterial thromboembolic events (RR 2.08, 95% CI 1.28 to 3.40; eight studies), but not for high-grade arterial thromboembolic events.

All-grade arterial thromboembolic events were significantly increased in patients with colorectal cancer (RR 2.79, 95% CI 1.42 to 5.49; three studies). High-grade arterial thromboembolic events were significantly increased with bevacizumab for patients with renal cell cancer (RR 5.14, 95% CI 1.35 to 19.64; three RCTs). The authors reported that risk of high grade arterial thromboembolic events was significantly increased with bevacizumab dose at 2.5mg/kg/week and 5mg/kg/week, but the relative risk for 5mg/kg per week (RR 1.50, 95% CI 0.84 to 2.69) suggested that this was not significant.

No publication bias was present.

Authors' conclusions

Addition of bevacizumab to standard antineoplastic therapy significantly increased the risk of arterial thromboembolic events, particularly cardiac ischaemia in cancer patients. The risk was similarly increased in patients who received both low and high doses of bevacizumab and may vary with tumour type: higher risks were associated with renal and colorectal cancer.

CRD commentary

The review addressed a clear question supported by defined inclusion criteria. Several sources were searched for relevant studies. It was unclear whether language restrictions were applied; language bias may have been present. Publication bias was assessed and was considered to be absent. This paper should be read in conjunction with Ranpura et al (see Publications of Related Interest). Appropriate methods were used to reduce potential for reviewer bias and error for data extraction, but it was unclear whether this extended to study selection and validity assessment. Trial quality was assessed using appropriate criteria, but limited details were reported. The included trials were considered to be of acceptable quality by the authors.

Trials were combined using meta-analysis and heterogeneity was explored, which appeared appropriate. Small numbers of studies were included for some comparisons and it was unclear whether the duration of follow-up was sufficient. All patients used concurrent therapy, but used different agents and this made it unclear whether it was bevacizumab dose or these differing agents that had an impact upon the results. The authors acknowledged the difference in definitions for grading adverse events and the patients had good organ function; thus findings may not be generalisable to patients with organ dysfunction.

The authors' conclusions reflected the evidence presented, but poor reporting of review methods and study quality should be borne in mind.

Implications of the review for practice and research

Practice: The authors stated that both physicians and patients should be aware of the cardiovascular side effects of bevacizumab and recommended consideration of prevention of arterial thromboembolic events in high-risk patients.
who received bevacizumab, including those aged over 65 years and those with a history of arterial thromboembolic events or patients with colorectal cancer or renal cell cancer.

Research: The authors stated that further studies were required to assess risk factors and underlying mechanisms for risk reduction.

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