Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis
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CRD summary
This review assessed the overall risk for venous thromboembolism in cancer patients associated with the use of bevacizumab. The authors concluded that the use of bevacizumab was significantly associated with an increased risk of developing venous thromboembolism in cancer patients receiving this drug. The authors' conclusions reflect the evidence presented and are likely to be reliable.

Authors' objectives
To assess the overall risk of venous thromboembolism (VTE) associated with the use of bevacizumab in cancer patients.

Searching
The electronic databases PubMed and Web of Science were searched from January 1966 until January 2008 to identify relevant studies written in English. Search terms were reported. Abstracts presented at the American Society of Clinical Oncology held between January 2000 and January 2008 were also searched for relevant studies.

Study selection
Eligible for inclusion in the review were phase 2 and phase 3 randomised controlled trials (RCTs) with a direct comparison between cancer patients treated with and without bevacizumab. Phase 1 trials and single arm phase 2 trials were excluded. For inclusion in the review patients had to be randomly assigned to bevacizumab treatment or control (placebo or best supportive care) in addition to concurrent therapy using a chemotherapeutic agent or a biological agent. Data including event or incidence of venous thromboembolism (VTE) and sample size needed to be available. Although not specifically stated in the inclusion criteria, outcomes of interest included: the incidence of all-grade VTE and the incidence of high-grade VTE. Grading of thromboembolisms were made by the authors of the review using the USA National Cancer Institutes common toxicity criteria (version 2 or 3). All-grade thromboembolisms were those ≥grade 2, whilst those ≥grade 3 were considered high-grade thromboembolisms. The type of malignancy varied between studies and included renal cell carcinoma, colorectal cancer, malignant mesothelioma, non-small cell lung carcinoma (NSCLC), pancreatic cancer and breast cancer. The dose of bevacizumab used in the studies was either 2.5mg/kg per week (defined as low dose) or 5mg/kg per week (defined as high dose). Concurrent medication also varied between studies.

Assessment of study quality
Study quality was assessed using criteria that included blinding of randomisation, completeness of follow up and objectivity of outcome measures. The authors did not state how the validity assessment was performed.

Data extraction
Data were extracted in order to calculate summary incidence rates, relative risks (RR) and 95% confidence intervals (CI). Two reviewers independently extracted data and any disagreements were resolved through consensus.

Methods of synthesis
Relative risk (RR) of VTE, influence of bevacizumab dose on the RR of VTE and the effect of tumour type on the RR of VTE were calculated. RRs were combined in a meta-analysis using both the fixed effects and random effects models. Analysis was performed using data from the number of patients available for analysis, rather than the number of patients enrolled in the trials. Heterogeneity was assessed using the Cochrane Q statistic and the I² test. Cochrane Q statistic with a p-value less than 0.10 was considered to demonstrate statistically significant heterogeneity. Where statistically significant heterogeneity was present, only results of the random effects model were reported. Causes of heterogeneity were explored. Publication bias was assessed using the Begg and Egger tests.

Results of the review
Fifteen RCTs were included in the meta-analysis (n=7,956 patients). Sample sizes ranged from 81 to 1,369 patients.
Publication bias was reported to be absent. Summary incidence of all-grade VTE (6 RCTs, n=2,279) was 11.9% (95% CI, 6.8,19.9). Heterogeneity was not reported. The summary incidence of high-grade VTE (13 RCTs, n=3795) was 6.3% (95% CI, 4.8,8.3) and statistically significant heterogeneity was reported (Q statistic=46.74, p<0.001, I squared=74.33). The summary RR of VTE (15 RCTs, n=7,956) for bevacizumab versus control was 1.33 (95% CI, 1.13, 1.56; p<0.001). The summary RR of all-grade VTE (6 RCTs, n=2,279) for bevacizumab versus control was 1.29 (95% CI, 1.03,1.63; p<0.001). The summary RR of high-grade VTE (13 RCTs, n=3,795) was 1.38 (95% CI 1.12, 1.70; p=0.002). Both high dose (5mg/kg per week) and low dose (2.5mg/kg per week) bevacizumab were associated with a statistically significant increase in the risk of VTE (RR, 1.31, 95% CI 1.02,1.68; p=0.4 and RR, 1.31, 95% CI 1.08, 1.60; p=0.007 respectively). The incidences and RR of both all-grade VTE and high-grade VTE with bevacizumab were found to vary among the different types of tumour, with the highest RR found in colorectal cancer and the lowest in renal cell cancer.

Authors' conclusions
The use of bevacizumab was significantly associated with an increased risk of developing VTE in cancer patients receiving this drug. The risk is increased with both high and low doses of bevacizumab.

CRD commentary
The review addressed a clear research question and was supported by adequate inclusion criteria. The search used a limited number of databases and was restricted to articles only in English, which means that relevant studies may have been missed. However, publication bias was assessed and found to be minimal. Details of the included studies were provided and the synthesis methods were appropriate and varied according to heterogeneity. However, no explanation was provided as to why data from 7956 patients rather than all 8448 patients enrolled in the studies were used in the analysis. It should also be noted that there was a slight discrepancy between the figure cited in the text and that given in the included RCT characteristics table for the number of patients analysed. The figure used in this review is taken from the text. In general, the review process was carried out with sufficient attempts to minimise errors and biases in most aspects, although it was not clear how the study selection process and validity assessment were performed. The authors' conclusions reflect the evidence presented and are likely to be reliable.

Implications of the review for practice and research
Practice: It may be appropriate to add a black box warning for VTE in the package insert of bevacizumab to raise awareness among physicians and patients. The high risk of VTE associated with aerodigestive cancer and mesothelioma suggest a need for prophylaxis in these patients when treated with bevacizumab.

Research: Studies are needed to investigate the prevention and management of VTE associated with bevacizumab.

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