Risk of venous and arterial thromboembolic events associated with anti-EGFR agents: a meta-analysis of randomized clinical trials
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CRD summary
The authors concluded that anti-epidermal growth factor receptor monoclonal antibodies (cetuximab and panitumumab) significantly increased the risk of venous but not arterial thromboembolism in patients with advanced cancer, particularly patients who received concomitant platinum-based chemotherapy. Given the unknown biases in the primary studies and uncertainty surrounding which treatments increased risk, the reliability of the conclusions remains uncertain.

Authors' objectives
To assess the risk of venous and arterial thromboembolic events in patients with advanced cancer and taking anti-epidermal growth factor receptor agents.

Searching
MEDLINE and EMBASE were searched without date restrictions for articles published in English. Search terms were reported. Relevant manufacturers’ package inserts were scanned.

Study selection
Eligible for inclusion were randomised (phase II or III) clinical trials that assessed the safety and effectiveness of anti-epidermal growth factor receptor agents (cetuximab, panitumumab, gefitinib and erlotinib) alone or in combination in patients with cancer. Outcomes of interest were venous and arterial thromboembolic events (as defined in the review).

Included trials were of patients with the following types of cancer: colorectal, non-small cell lung, head and neck, renal, and gastroesophageal. The median age of patients ranged from 56 to 74 years. Where reported, the median duration of anti-epidermal growth factor receptor treatment ranged from three to 11 cycles. Two trials used higher than currently approved doses of agents. Where reported, the median duration of chemotherapy ranged from five to 17 cycles. Most trials administered anti-epidermal growth factor agents with chemotherapy and compared these to controls (chemotherapy with or without placebo). Median progression-free survival rates were reported by some trials.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
The authors did not state that they assessed trial quality.

Data extraction
Two reviewers independently extracted the number of venous and arterial thromboembolic events to calculate proportions and ultimately to calculate relative risks and 95% confidence intervals. Median progression-free survival rates (in months) were extracted.

Discrepancies were resolved through consensus.

Methods of synthesis
A fixed-effect model, or random-effects model where there was evidence of statistical heterogeneity, was used to combine relative risks (RRs) and 95% confidence intervals (CIs).

Statistical heterogeneity was assessed using Cochran’s Q and I² statistics. Subgroup analyses were conducted based on underlying malignancy and class of anti-epidermal growth factor receptor agent used: monoclonal antibodies (cetuximab and panitumumab) versus oral tyrosine kinase inhibitors (erlotinib and gefitinib).

Meta-regression was carried out to assess differences in median length of treatment in treatment and control groups. Exploratory analyses were conducted to assess trials with improved outcomes (cetuximab and panitumumab trials) and...
trials that included a cisplatin combination.

Publication bias was assessed using Begg's funnel plots, Begg and Egger's tests and the trim and fill method.

**Results of the review**

Thirteen trials (7,611 patients; calculated as 7,420 analysed) were included in the review. Where reported, median progression-free survival generally tended to be longer in arms that included the anti-epidermal growth factor receptor agent.

**Venous thromboembolic events (11 trials):** Anti-epidermal growth factor receptor agents were associated with a statistically significantly higher risk of developing venous thromboembolic events compared to controls (RR 1.37, 95% CI 1.11 to 1.69); there was a slight discrepancy between figures reported in the text and forest plot and these are the forest plot figures. There was no evidence of statistical heterogeneity ($I^2=0\%$).

Subgroup analyses by underlying malignancy resulted in no statistically significant differences between treatment groups. Subgroup analyses by class of drug showed that differences remained significantly different in trials of monoclonal antibodies but differences were not significant in trials of oral tyrosine kinase inhibitors. Meta-regression indicated that length of treatments did not result in statistically significant differences between treatment groups (eight trials).

**Arterial thromboembolic events (five trials):** There were no statistically significant differences between treatment groups in the risk of arterial thromboembolic events. Statistical heterogeneity was not significant ($I^2=42\%$).

Subgroup analyses by class of anti-epidermal growth factor receptor agent did not significantly alter the findings. Analyses by underlying malignancy indicated statistically significant differences in patients with head and neck cancer (RR 2.39, 95% CI 1.24 to 4.62) with greater risk of arterial thromboembolic events in the treatment group.

Risk differences and results from exploratory analyses were reported in the review. There was no evidence of publication bias using any methods.

**Authors’ conclusions**

Anti-epidermal growth factor receptor monoclonal antibody agents (cetuximab and panitumumab) significantly increased the risk of venous but not arterial thromboembolism in patients with advanced cancer, particularly in patients who received combined anti-epidermal growth factor receptor monoclonal antibody agents and platinum-based chemotherapy.

**CRD commentary**

The review question was clear and was supported by clear inclusion criteria. Only two electronic databases were searched and as this was restricted to publications in English potentially relevant data may have been missed. The quality of the trials was not assessed so there was uncertainty around how robust the findings were. It was unclear whether screening of studies was conducted in duplicate so reviewer error and bias could not be ruled out.

Combination chemotherapies and control treatments varied considerably so it was unclear whether pooling of the data was appropriate. It was not possible to separate the effects of the anti-epidermal growth factor receptor agents from the chemotherapies with which they were combined so it was unclear which treatments increased risk; the authors acknowledged this. The authors acknowledged that the incidence of venous thromboembolic events may be under-reported in trials. The evidence on arterial thromboembolic events was limited.

Given the unknown biases in the primary studies, uncertainty surrounding which treatments increased the risk of events and other limitations, the reliability of the conclusions remains uncertain.

**Implications of the review for practice and research**

**Practice:** The authors stated that clinicians should be aware of the increased risk of venous thromboembolism, especially in patients with colorectal and head and neck cancer, where these drugs are currently indicated. They also stated that patients in the review had adequate major organ function and the results may not be generalisable to patients with organ dysfunction.
Research: The authors stated that the evidence from the review could be used as the basis for testing thromboprophylaxis in an appropriate clinical trial setting and also stimulate a retrospective analysis of outcomes in patients who developed venous thromboembolic events.

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