A meta-analysis and systematic review of the efficacy and safety of anticoagulants as cancer treatment: impact on survival and bleeding complications

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**CRD summary**
The authors concluded that anticoagulants, especially low molecular weight heparin, significantly increase survival in cancer patients without venous thromboembolism, but also increase the risk of bleeding. However, anticoagulants cannot be recommended as a cancer treatment until further research confirms these results. This was a well-conducted and clearly presented review, and the authors’ conclusions are likely to be reliable.

**Authors' objectives**
To evaluate the effects of anticoagulants on survival and safety in cancer patients without venous thromboembolism.

**Searching**
MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, the Cochrane CENTRAL Register, DARE, National Guideline Clearinghouse and conference proceedings of three specified societies were searched to the end of 2006; the search terms were reported. In addition, the references from included studies, relevant reports and guidelines were screened and experts were contacted. Abstracts were only included if they had been presented at a major international conference within the last 3 years. No language restrictions were applied.

**Study selection**
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review. Where reported, the average duration of follow-up in the included studies ranged from 6 to 69 months.

Specific interventions included in the review
Studies that compared anticoagulant drug therapy with an appropriate control treatment were eligible for inclusion. Anticoagulant treatment had to be with low molecular weight heparin (LMWH), unfractionated heparin (UFH) or an oral vitamin K antagonist. Treatment had to be given continuously for more than 4 weeks unless its cessation was clinically indicated. Studies of indwelling catheters, surgery, intraportal heparin infusions or combinations of anticoagulants were excluded, as were studies that used different concurrent treatments in the treatment arms. Most of the studies evaluated LMWH or warfarin.

Participants included in the review
Studies of adults with cancer who did not have a concurrent diagnosis of venous thromboembolism were eligible for inclusion. All of the included studies were in patients with solid tumours (including breast cancer, lung cancer and mixed tumour types).

Outcomes assessed in the review
Studies that assessed overall mortality as a planned primary or secondary outcome were eligible for inclusion. The primary review outcomes were 1-year overall mortality and all bleeding complications. The secondary outcomes were major bleeding (as defined by the study authors) and fatal bleeding.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed and scored using the Jadad scale, which considers the randomisation method, blinding and description of withdrawals. Studies scoring 3 or more out of the maximum 5 points were considered to be good quality. Two reviewers independently assessed study validity; any disagreements were resolved through consensus and third-party adjudication.
Data extraction
Two reviewers independently extracted the data and resolved any disagreements through consensus with the aid of a third reviewer. The cumulative proportions of patients experiencing the events of interest were extracted or estimated from survival curves.

Methods of synthesis
How were the studies combined?
Pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated using the fixed-effect Mantel-Haenszel method in the absence of significant heterogeneity and the DerSimonian and Laird random-effects model in its presence (p<0.10). Publication bias was assessed using a funnel plot and was tested using the rank correlation test of Begg and Mazumdar and the regression asymmetry test of Egger.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Cochran Q statistic and the I-squared statistic. The analyses were repeated using random-effects models. Subgroup analyses and meta-regression were planned to examine the influence of the type of anticoagulant, study quality, length of treatment, type of control group, type of cancer, stage of disease and use of chemotherapy in all patients. Differences between LMWH and warfarin were examined by comparing the ratio of the RRs; the absolute risk differences (ARDs) in mortality for LMWH and warfarin were also calculated.

Results of the review
Eleven RCTs (n=3,343) were included. Six RCTs evaluated LMWH (n=1,801), four evaluated warfarin (n=1,265) and one evaluated UFH (n=277).

Three studies scored 2 or less for quality on the Jadad scale. Two studies scored 5 points and two used an intention-to-treat analysis. Two studies were not evaluable and 6 studies scored 3 or more and were considered to be good quality. Quality criteria were reported for the individual studies.

No significant heterogeneity was found for 1-year mortality and bleeding complications. The results from fixed-effect models are reported.

There was a statistically significant reduction in 1-year overall mortality among patients allocated to anticoagulants compared with control treatments (RR 0.905, 95% CI: 0.847, 0.967, p=0.003). The reduction in 1-year mortality was significant for studies of LMWH (RR 0.877, 95% CI: 0.789, 0.975, p=0.015), but there was no significant difference between warfarin and control treatments (p=0.239). There was no significant difference between UFH and the control treatment in the one study evaluating UFH. There was no significant difference between LMWH and warfarin in 1-year mortality (p=0.418); the ARDs were 8.0% and 3%, respectively.

There was a statistically significant increase in all bleeding complications among patients allocated to anticoagulants compared with control treatments (RR 2.309, 95% CI: 1.928, 2.764, p<0.0001). The increase in bleeding complications was significant for LMWH (RR 2.029, 95% CI: 1.205, 3.417, p=0.008) and warfarin (RR 2.366, 95% CI: 1.954, 2.866, p<0.0001). There was no significant difference between UFH and the control treatment in bleeding complications in the one study evaluating UFH. There was a significantly greater increase in bleeding complications in patients allocated to warfarin compared with LMWH; the ARD was 22.5% versus 2.4% (p<0.0001).

There was a statistically significant increase in major bleeding complications among patients allocated to anticoagulants compared with control treatments (p<0.0001). The increase in major bleeding complications was significant for warfarin (p<0.0001) but not LMWH (p=0.128).

There was no significant difference between anticoagulants and control treatments in fatal bleeding complications (0.49% versus 0.17%, p=0.542). None of the studies reported any cases of fatal pulmonary embolism.

There was no evidence of publication bias.

Other results were also reported.
Authors' conclusions
Anticoagulants, especially LMWH, significantly increase survival in cancer patients without venous thromboembolism, but also increase the risk of bleeding. However, anticoagulants cannot be recommended as a cancer treatment until further research confirms these results.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to minimise publication and language bias; the potential for publication bias was assessed and no evidence of it was found. Validity was assessed using specified criteria and the results of this assessment reported. Methods were used to minimise reviewer errors and bias in the extraction of data and assessment of validity, but it was not clear whether similar steps were taken at the study selection stage. The studies were appropriately combined in meta-analyses, statistical heterogeneity was assessed, and the influence of various variables was examined. This was a well-conducted and clearly presented review, and the authors’ conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that anticoagulants cannot be recommended as a treatment for cancer until further research confirms the review findings.

Research: The authors stated that there is a need for further good-quality, adequately powered RCTs to confirm the review findings before anticoagulants can be recommended as a cancer treatment.

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