Major bleeding rates after prophylaxis against venous thromboembolism: systematic review, meta-analysis, and cost implications

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CRD summary
This review compared major bleeding using different thromboprophylactic agents during major orthopaedic surgery. The authors concluded that low molecular weight heparins reduce bleeding events in comparison with unfractionated heparins and pentasaccharide, but increase them in comparison with warfarin and other coumarin derivatives. It is not possible to judge the robustness of these conclusions given the limited reporting of individual study details.

Authors' objectives
To compare rates of major bleeding among different thromboprophylactic agents used to prevent venous thromboembolism in patients undergoing major orthopaedic surgery.

The review also assessed the consequences and estimated the costs of managing episodes of major bleeding, but this abstracts only refers to the effects on major bleeding.

Searching
The following sources were searched in September 2001: MEDLINE, PubMed, EMBASE, the Cochrane Library, OLDMEDLINE, the National Research Register, Medical Research Council database of trials, the Science Citation Index; HTA, Current Controlled Trials, NHS EED, EconLit and DARE. Full details of the search strategy and protocol are available on request from the authors.

Study selection
Controlled trials were eligible for inclusion.

Specific interventions included in the review
Studies that compared at least two of the following thromboprophylactic agents were eligible for inclusion: low molecular weight heparin (LMWH), warfarin or another coumarin derivative (WARF), unfractionated heparin (UFH), or pentasaccharide (PS). The studies had to use currently licensed doses and recommended thromboprophylaxis regimens. All included studies reported direct comparisons between LMWH and one of the other regimens.

Participants included in the review
Studies of patients undergoing major orthopaedic surgery were eligible for inclusion. Major orthopaedic surgery was defined as total hip or knee replacement, or hip fracture surgery.

Outcomes assessed in the review
Studies that reported major bleeding during the acute phase of hospitalisation, with up to 14 days' follow-up, were eligible for inclusion. The secondary outcomes were total 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
The studies were assessed for details of randomisation, blinding and reporting of withdrawals. One reviewer assessed validity and this was checked by a second reviewer. Any differences were resolved by consensus.
Data extraction
One reviewer extracted the data and this was checked by a second reviewer. Any differences were resolved by consensus. Data for major bleeding were extracted using the definition for major bleeding of Hull et al. (details were reported). Where this was not reported, attempts were made to estimate it from data presented, or the authors’ definition was used. A Bleeding Index of greater than 2 was accepted as denoting major bleeding.

Methods of synthesis
How were the studies combined?
Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using a fixed-effect model (Mantel-Haenszel) for separate comparisons of WARF, UFH and PS with LMWH. The data were also pooled using a random-effects model (DerSimonian and Laird). Publication bias was assessed using funnel plots.

How were differences between studies investigated?
Sensitivity analyses were used to examine the influence on the results of study quality, publication status, study size (300 or more patients) and source of funding. Statistical heterogeneity was explored using L’Abbe plots, and an influence analysis was used to examine the effects of individual studies on the pooled estimates.

Results of the review
Twenty-one studies (n=20,523) were included.

WARF significantly reduced the risk of major bleeding compared with LMWH (RR 0.59, 95% CI: 0.44, 0.80) (7 published studies).

UFH significantly increased the risk of major bleeding compared with LMWH (RR 1.52, 95% CI: 1.04, 2.23) (9 published studies and 1 unpublished study).

PS significantly increased the risk of major bleeding compared with LMWH (RR 1.52, 95% CI: 1.11, 2.09) (4 published studies).

Statistically significant heterogeneity was not found in any of the analyses (P>0.10).

L’Abbe plots showed no clear outliers and there was no evidence of publication bias (symmetrical funnel plot and P>0.10 for asymmetry). The results were similar after excluding each study in turn. Study quality, publication type, study size and source of funding had little effect on the results.

Fatal bleeding was rare (0.01% overall treated patients).

Cost information
The review also assessed the costs of managing major bleeding. The authors estimated that the average cost of managing major bleeding was US$113 per patient receiving thromboprophylaxis.

Authors’ conclusions
LMWH reduced major bleeding in comparison with UFH and PS, but increased bleeding events in comparison with WARF.

CRD commentary
The review question was clear in terms of the study design, participants, intervention and outcomes. Many relevant sources were searched but, as the authors acknowledged, they might have missed studies published in languages other than English. Attempts were made to locate unpublished data, thus minimising the potential for publication bias, and the potential for publication bias was assessed. Methods were used to minimise errors and bias in the assessment of validity and extraction of data, but it was unclear whether similar steps were taken in the study selection process. Validity was...
assessed using specified established criteria, although the quality of the included studies was not reported.

Statistical heterogeneity was assessed and the data were combined in a meta-analysis. Sensitivity analyses examined the effect on pooled results of various factors including study quality. It was difficult to assess the appropriateness of the analyses as details of the individual studies were not presented, and it was unclear whether the included studies were randomised or non-randomised controlled trials. Given these limitations in reporting, it is not possible to judge the robustness of the authors' conclusions.

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

Practice: The authors stated that data on the different rates of major bleeding between classes of antithrombotic agents, as well as the costs of managing bleeding, should be taken into account when selecting the appropriate method of thromboprophylaxis.

Research: The authors did not state any implications for further research.

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