
Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency

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CRD summary

This well-conducted review assessed anti-Xa heparin levels and bleeding events in patients with severe renal insufficiency who were receiving low molecular weight heparin. It concluded that standard therapeutic doses of enoxaparin led to higher anti-Xa heparin levels and increased the risk of major bleeding. These conclusions are limited by the observational nature of the included studies.

Authors' objectives

To compare levels of anti-Xa heparin and the risk of bleeding in patients with a creatinine clearance of up to 30 mL/minute (mL/min), who were being treated with low molecular weight heparin (LMWH), with those with a creatinine clearance greater than 30 mL/min.

Searching

MEDLINE and EMBASE (both from inception to November 2005) and the Cochrane Library (Issue 4, 2005) were searched; all search terms were reported. No language restrictions were applied. The references of retrieved articles were checked and experts were contacted for additional studies.

Study selection

Study designs of evaluations included in the review

Studies of any design with more than 10 patients were eligible for inclusion. Included in the review were subgroups of patients from randomised controlled trials (RCTs), and prospective and retrospective cohort studies.

Specific interventions included in the review

Studies that administered at least one dose of LMWH were eligible for inclusion in the review. Standard weight-adjusted therapeutic doses, empirically-adjusted doses, or prophylactic doses of LMWH were all eligible for inclusion. Studies of intravenous LMWH or more than one LMWH preparation or dose were excluded. Only commercially available LMWHs (enoxaparin, tinzaparin and dalteparin) were included in the review.

Participants included in the review

Studies that included patients with varying degrees of renal function, including those with a creatinine clearance of up to 30 mL/min, were eligible for inclusion. Patients who were dependent on dialysis were excluded from the review.

Outcomes assessed in the review

Studies that assessed anti-Xa heparin levels or major bleeding were eligible for inclusion in the review.

How were decisions on the relevance of primary studies made?

Two reviewers independently assessed the studies for relevance, and any disagreements were resolved by discussion.

Assessment of study quality

Studies were assessed using the following criteria: consecutive patient enrolment, duration and completeness of follow-up for major bleeding, and whether bleeding was assessed objectively and reproducibly using a priori definitions. Two reviewers independently assessed the studies for validity. The reviewers were not blinded to the identity of the studies.

Data extraction

Two reviewers extracted the data independently, and any disagreements were resolved by discussion. Peak anti-Xa levels 4 hours after the injection of LMWH were extracted. Maximum LMWH activity was considered to be equivalent to the 4 hour anti-Xa level. Data on major bleeding events were extracted and the authors' definitions were adopted. Authors were contacted to obtain data where a threshold other than creatinine clearance of up to 30 mL/min was used to define severe renal failure, where only mean creatinine clearance was reported, or where other relevant data were not reported. For each study, odds ratios (ORs) were calculated for major bleeding events in patients with and without severe renal insufficiency.

Methods of synthesis

How were the studies combined?

The results for anti-Xa levels were presented as a narrative synthesis. ORs for major bleeding events in patients with and without severe renal insufficiency were pooled in a meta-analysis using the fixed-effect Peto method. A pooled risk difference and 95% confidence interval (CI) were presented. Publication bias was assessed using a funnel plot, although details of the analysis were not provided.

How were differences between studies investigated?

Differences between the studies in the study design, type and dose of LMWH, and measurement of creatinine clearance and anti-Xa levels were explored narratively. For major bleeding events, statistical heterogeneity was assessed using the I-squared statistic and chi-squared test. In addition, two a priori subgroup analyses for type and dose of LMWH were carried out, and an a priori sensitivity analysis was conducted to assess the effect of including only high-quality studies.

Results of the review

Eighteen studies (n=6,081) were included in the review. These comprised two subgroups of patients from RCTs (n=3,934), 12 prospective cohort studies (n=1,320) and 4 retrospective cohort studies (n=827).

Study quality.

Twelve of the 14 prospective studies had consecutive enrolment of the patients. The mean follow-up varied from 5 to 45 days in the prospective studies, but could not be determined for retrospective studies or those measuring only anti-Xa-levels. Ten of the 12 studies reporting bleeding outcomes used a priori definitions of major bleeding.

Anti-Xa measurements.

Ten studies used enoxaparin and assessed anti-Xa levels. Four studies used a therapeutic dose, three used an empirically adjusted dose and three a prophylactic dose. In three of the therapeutic dose studies, levels of anti-Xa were statistically significantly higher in patients with a creatinine clearance of up to 30 mL/min.

Two studies used tinzaparin at therapeutic doses and assessed levels of anti-Xa. Neither study found a correlation between the peak level of anti-Xa and creatinine clearance.

One study used dalteparin and assessed levels of anti-Xa. No difference between patients with renal insufficiency and those with normal renal function was found.

Major bleeding events.

Twelve studies (n=4,971) reported major bleeding events. Ten evaluated enoxaparin (n=4,741) and two evaluated tinzaparin (n=230). For all studies, severe renal insufficiency (a creatinine clearance of up to 30 mL/min) was associated with an increased risk of major bleeding (pooled OR 2.25, 95% CI: 1.19, 4.27). A sensitivity analysis excluded 2 studies that did not meet the quality criterion of using a priori definitions of bleeding. This showed an increased risk of bleeding in patients with renal insufficiency (OR: 2.17, 95% CI: 1.14, 4.16).

The pooled OR for studies using enoxaparin also showed an increased risk of major bleeding for patients with severe renal insufficiency (OR 2.59, 95% CI: 1.34, 5.01).

Studies using a therapeutic dose of enoxaparin also showed an increased risk of major bleeding for patients with severe renal insufficiency (pooled OR 3.88, 95% CI: 1.78, 8.45).

Studies using empirically adjusted doses of enoxaparin did not show any difference between patients with and without severe renal insufficiency (pooled OR 0.58, 95% CI: 0.09, 3.78).

Authors' conclusions

Non-dialysis-dependent patients with a creatinine clearance of 30 mL/min or less have elevated levels of anti-Xa and an increased risk of a major bleeding event when treated with standard therapeutic doses of enoxaparin. However, no conclusions could be drawn for other LMWHs.

CRD commentary

The review question and the inclusion criteria were clear. The search involved relevant databases and efforts were made to identify unpublished studies. This, together with the lack of language restrictions, reduces the likelihood that language or publication bias was introduced into the review. The authors concluded that publication bias might have been present but did not report the results of any assessment. However, they stated that any possible bias probably underestimates the risk of bleeding. The authors used appropriate and rigorous methods to reduce the possibility of bias or error in the study selection, validity assessment and data extraction processes. An appropriate validity assessment was conducted and this was used to inform an a priori sensitivity analysis.

The decision to employ a combination of narrative synthesis and meta-analysis was appropriate, and suitable methods were used to explore sources of heterogeneity between the studies. This appears to have been a well-conducted review, although the clinical differences and observational nature of the included studies indicate the need for caution when interpreting the results.

Implications of the review for practice and research

Practice: The authors stated that adjusted doses of LMWH may reduce the elevated risk of bleeding in patients with renal insufficiency.

Research: The authors stated that randomised trials should be conducted to determine the optimal anticoagulant strategy for patients with renal insufficiency. Future research should also assess the pharmacokinetic profiles of different LMWHs in patients with different degrees of insufficiency to better assess the risk of bleeding events.

Bibliographic details

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Other publications of related interest

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000;283:2008-12.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.