Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism

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CRD summary
The authors concluded that case-fatality rates of recurrent venous thromboembolism and major bleeding events were similar in the initial six-month period of anticoagulation treatment. Case-fatality rates appeared to decrease when treatment was completed. The authors’ conclusions reflected the evidence presented and are likely to be reliable.

Authors’ objectives
To evaluate case-fatality rates of recurrent venous thromboembolism (VTE) and major bleeding events during anticoagulation, and the case-fatality rate of major recurrent VTE after anticoagulation.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and all EBM Reviews were searched up to 2008. Relevant journals and reference lists of reviews and included studies were handsearched for further articles. There were no language or publication restrictions. Search terms were reported.

Study selection
Prospective studies of consecutive patients with objectively confirmed symptomatic deep venous thrombosis (DVT) or pulmonary embolism (as defined in the paper) and objectively confirmed recurrent events were eligible for inclusion in the review.

Patients had to receive five days of initial treatment with unfractionated heparin (intravenous, adjusted-dose or weight-based subcutaneous), low-molecular-weight heparin (LMWH: intravenous or weight-based subcutaneous), fondaparinux, idraparinux or ximelagatran. Patients also had at least three months of anticoagulant treatment that comprised vitamin K antagonist (target international normalised ratio 2.0 to 3.0), unfractionated heparin (weight-based or adjusted-dose), LMWH (subcutaneous weight-adjusted or fixed-dose), idraparinux or ximelagatran.

Studies had to include at least one primary outcome: fatal recurrent VTE or fatal major bleeding event; or secondary outcomes (probable fatal recurrent VTE, recurrent nonfatal VTE and major bleeding events). Definitions were given in the paper.

Most of the included studies administered intravenous unfractionated heparin or subcutaneous LMWH combined with a vitamin K antagonist. Fatal recurrent VTE was poorly defined and not objectively assessed in a large proportion of studies (although independent adjudication for the latter was employed in many cases).

Two reviewers independently selected studies for inclusion. Discrepancies were resolved by reference to a third reviewer.

Assessment of study quality
Study quality was assessed by two independent reviewers using Cochrane Risk of Bias tool for randomised controlled trials (RCTs) and Newcastle-Ottawa Quality Assessment Scale for observational studies.

Discrepancies were resolved by reference to a third reviewer.

Data extraction
Data were extracted in order to report event rates and 95% confidence intervals (CI) for primary outcomes. Data were converted to rates per patient-month of mean or median follow-up for the meta-analysis. Intention-to-treat data were used.
Data were extracted independently by two reviewers. Discrepancies were resolved by reference to a third reviewer.

**Methods of synthesis**
The transformed weighted event rates and 95% CIs were pooled in a meta-analysis using the DerSimonian-Laird random-effects model. Results were stratified by DVT, pulmonary embolism or any VTE and during the initial stage of anticoagulant treatment (three to six months) and after anticoagulation treatment (reported as per 100 patient-years without anticoagulation).

Statistical heterogeneity was assessed using the $I^2$ statistic (<25% was considered low heterogeneity, 25% to 50% moderate heterogeneity and over 50% high heterogeneity).

Sensitivity analyses were conducted by exclusion of patients who received initial idraparinux or ximelagatran and by inclusion only of patients who received vitamin K antagonist for at least three months.

**Results of the review**
Sixty-nine studies (56 RCTs and 13 prospective cohort designs) were included in the review. More than half of the RCTs had adequate randomisation and allocation concealment. Most RCTs were unblinded. Complete outcome reporting was available in most trials. All observational studies were reported to be adequately representative with sufficient follow up.

**Fatal recurrent VTE**: During the first three months of treatment, rate of fatal recurrent VTE was 0.4% (95% CI 0.3% to 0.6%) with moderate heterogeneity ($I^2=33\%$) and the case-fatality rate of recurrent VTE was 11.3% (95% CI 8.0% to 15.2%) with high heterogeneity ($I^2=61.9\%$) in patients (n=19,027) who initially presented with VTE. Secondary outcomes and sensitivity analyses were reported to produce similar estimates.

Following treatment, rate of recurrent VTE was 0.3 per 100 patient years (95% CI 0.1 to 0.4) with low heterogeneity ($I^2=10\%$) and the case-fatality rate was 3.6% (95% CI 1.9% to 5.7%) with high heterogeneity ($I^2=68\%$) in patients (n=47,663) who initially presented with VTE. The authors stated that it was not possible to determine outcomes following treatment in patients who initially presented with pulmonary embolism or pulmonary embolism with or without DVT.

**Fatal bleeding events**: During the first three months of treatment, rate of fatal bleeding events was 0.2% (95% CI 0.1% to 0.3%) with moderate heterogeneity ($I^2=28.6\%$) and the case-fatality rate was 11.3% (95% CI 7.5% to 15.9%) with low heterogeneity ($I^2=16\%$) in patients (n=19,027) who initially presented with VTE. There was no statistical difference in these outcomes between patients with initial DVT or pulmonary embolism. The authors stated that it was not possible to determine the case-fatality rate after six months of treatment in patients with pulmonary embolism.

**Authors' conclusions**
Case-fatality rates of recurrent VTE and major bleeding events were similar in the initial six month period of anticoagulation treatment. Case-fatality rates appeared to decrease when treatment was completed.

**CRD commentary**
The review question was clear and supported by detailed and potentially reproducible inclusion criteria. The search strategy appeared to include several relevant sources. Efforts were made to minimise language and publication biases. The review process was carried out with adequate attempts to avoid bias and error. Appropriate quality assessments were carried out for different included study designs. Study details were provided, although there was little data on patient characteristics. The chosen method of synthesis appeared to be appropriate given reported heterogeneity in some analyses. The authors' conclusions reflected the evidence presented and are likely to be reliable.

**Implications of the review for practice and research**
**Practice**: The authors stated that case-fatality rates combined with absolute rates of recurrent VTE and major bleeding events provided a surrogate measure of mortality that should be considered in different management strategies for
patients with VTE.

Research: The authors stated that future studies should consider patients with DVT and pulmonary embolism separately when estimating all-cause mortality. Subgroup analyses of patients with unprovoked VTE at high or low risk for recurrent VTE were needed.

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Record Status
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.