CRD summary
This review found that the risks of haemorrhage and thromboembolism were minimised at an international normalised ratio of two to three; moderately higher ratios appeared to be safe and more effective than lower ones. Significant heterogeneity and possible missed studies mean that the reliability of the authors' conclusions is unclear.

Authors' objectives
To evaluate the effects of anticoagulation intensity on the risks of haemorrhage and thromboembolism.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL were searched for articles included up to 2006. References in the Science Citation Index were searched. The search terms were reported in an online appendix.

Study selection
Studies of patients who were on anticoagulant therapy were eligible for inclusion if they reported the number of haemorrhages or thromboembolisms that occurred and the person-years of observation, using at least three ranges for the patients' international normalised ratios (INRs), which were under two, two to three, and over three.

The included studies were conducted in patients with various indications for anticoagulant therapy. Where reported, the drugs used were warfarin, phenprocoumon, and acenocoumarol. Anticoagulant use was started before, at the start of, or during the studies. Forty-four percent of the patients were female.

The number of reviewers who selected studies was not reported.

Assessment of study quality
Methodological quality was assessed using criteria for assigning events to a particular range, number of events not assigned to a range, follow-up methods used to identify events, method of imputation to calculate the person-years of observation, and whether measurements taken outside the study centre were included. Quality assessment was performed by two reviewers, with disagreements resolved by committee.

Data extraction
The data were extracted for patients who received anticoagulant therapy alone and not with antiplatelet medication. The number of haemorrhages and thromboembolisms that occurred in patients in each range of ratios, the types of events, and the criteria used were extracted. If the events were reported by severity, all except those classified as minor were extracted. The person-years of observation were extracted for each range of ratios. The rates of haemorrhage and thromboembolism were grouped into four ranges of INR, under two, two to three, three to five, and over five, and divided by the person-years of observation for that range. The relative and absolute risks of haemorrhagic, thrombolytic, and combined events were calculated, using the range two to three as a reference.

Two reviewers extracted the data and disagreements were resolved by committee.

Methods of synthesis
The studies were weighted by the logarithm of their total person-years of observation for each INR range. The 95% confidence intervals for the pooled absolute and relative risks and were calculated using critical values based on the Poisson distribution. A negative binomial regression model was used to calculate the risks of haemorrhagic, thromboembolic, and combined events for the INR ranges. The summary rates of thromboembolic events were
recalculated after grouping by the most common indication for anticoagulation.

Heterogeneity was assessed using the Breslow-Day test. Sensitivity analyses were performed by: restricting the analysis to studies that only assessed severe haemorrhagic events; restricting to those that assessed patients requiring anticoagulation for atrial fibrillation, venous thromboembolism, or artherosclerosis; imputing the number of events that occurred when the INR exceeded five, in studies that only reported them for a ratio over three; excluding studies that reported the most events; and assessing the possible interactions between the INR and the event risk with possible confounders.

**Results of the review**

Nineteen studies were included (n=80,713 patients, range 55 to 42,451); six were randomised controlled trials (n=4,803), three were prospective cohort studies (n=6,393), and 10 were retrospective cohort studies (n=69,517). Thirteen studies reported ranges of international normalised ratios that matched the four categories in this review. Twelve studies used follow-up visits to identify events, four used medical records, and three used administrative databases. Four studies used the ratios measured at the time of the event to assign events to a range and 15 used previous measurements. The person-years of observation were measured using linear interpolation in 15 studies and four used equidivision. Only three studies captured all the measures of ratios, including those outside regular clinic.

**Haemorrhagic events:** Compared with ratios of two to three, the risk of events significantly increased with a ratio of three to five (RR 2.7, 95% CI 1.8 to 3.9; absolute risk 3.7% per year, 95% CI 2.25 to 6.3) and with ratios over five (RR 21.8, 95% CI 12.1 to 39.4; absolute risk 30.1% per year, 95% CI 14.9 to 60.9). There was no significant difference with ratios under two.

**Thromboembolic events:** The risk of thromboembolism was significantly increased with a ratio under two (RR 3.5, 95% CI 2.8 to 4.4; absolute risk 2.6% per year, 95% CI 1.8 to 3.6) and with ratios over five (RR 2.6, 95% CI 1.3 to 5.1; absolute risk 6.6% per year, 95% CI 3.2 to 13.9). There was no significant difference with ratios of three to five.

**Combined events:** An INR of two to three was associated with significantly fewer events than all of the other ranges of ratios (absolute risk 4.3% per year, 95% CI 3.0 to 6.3). The next safest ratio was three to five (RR 1.8, 95% CI 1.2 to 2.6); the risk of an event was lower at this ratio than at a ratio under two, but this was not significant.

Significant heterogeneity was reported for studies of both types of events (p<0.001) and the sensitivity analyses showed similar results.

**Authors’ conclusions**

The risks of haemorrhage and thromboembolism were minimised at an INR of two to three. Ratios that were moderately higher than this therapeutic range appeared to be safe and more effective than lower ratios.

**CRD commentary**

The review question was supported by inclusion criteria for participants, intervention, and outcomes, but there were none for study design. Relevant databases were searched, but the use of language restrictions was not reported and the risk of language bias cannot be assessed. No attempts to locate unpublished studies were reported, so publication bias was possible. The validity assessment and data extraction were conducted by two reviewers, reducing possible error and bias; similar steps were not reported for study selection. The quality criteria did not assess aspects of the study design, but the aspects that were assessed were taken into consideration in the analysis. There was significant heterogeneity in the analyses.

This heterogeneity and the possibility of missing relevant studies mean that the reliability of the authors’ conclusions is unclear.

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

**Practice:** The authors did not state any implications for practice.
Research: The authors stated that researchers should continue to evaluate interventions, such as anticoagulation clinics, patient self management, and telephone communication systems, that increase the amount of time that a patient's INR is within the therapeutic range.

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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.