Effect of study setting on anticoagulation control: a systematic review and metaregression
van Walraven C, Jennings A, Oake N, Fergusson D, Forster AJ

CRD summary
This review assessed the effect of study characteristics on anticoagulation control in patients given anticoagulation drugs. The authors concluded that patients from community practices had worse anticoagulation control than patients from anticoagulation clinics and patients taking part in clinical trials. The differences observed could have been influenced by other factors that were not studied.

Authors' objectives
To describe studies of anticoagulation control and to determine study level factors that significantly influence anticoagulation control, in particular the effect of study setting.

Searching
MEDLINE was searched; the search strategy was reported but not the dates covered. Searches of EMBASE and Web of Science and handsearches were also undertaken, but no methods were reported. The search was limited to studies published in the English language.

Study selection
Study designs of evaluations included in the review
RCTs and cohort studies in which at least one patient group received OAC therapy were eligible for inclusion. Studies of less than 25 patients and studies with less than 3 weeks’ follow-up were excluded. The included studies were described as prospective or retrospective. No other information about the study design was reported.

Specific interventions included in the review
The implicit criterion for inclusion was studies of oral anticoagulants (OACs). In the case of randomised controlled trials (RCTs), those comparing OAC therapy with other therapies were eligible. Warfarin was the anticoagulant used in most of the included studies; others were acenocoumarol and phenprocoumon. Control group data were not used in this review.

Participants included in the review
The implicit criterion for inclusion was patients on anticoagulation therapy. The most common indication for anticoagulation in the included studies was atrial fibrillation. Most studies included more than one indication; other indications were venous thromboembolism, other cardiovascular disease, peripheral vascular disease and valvular heart disease. Most of the included study groups were from anticoagulation clinics (68.3%) or community practices (24.4%), with a minority from clinical trials (7.3%). A minority of the study groups (5.7%) were self-monitoring patients. No other information about the participants was reported.

Outcomes assessed in the review
Studies that assessed anticoagulation control through monitoring of the international normalised ratio (INR) over time were eligible for inclusion. The studies had to report a therapeutic target INR ranging from between 1.8 to 2.0 (lower limit) and 3.0 to 3.5 (upper limit). Only studies that used a patient-time approach to measure the percentage of time spent in the target therapeutic range were included. Studies that measured serial INRs after administration of vitamin K were excluded. Studies that reported unconventional statistics for anticoagulation control, such as the proportion of patients above a particular threshold, were also excluded. The median follow-up in the included studies was 122.9 patient-years (range: 22.7 to 509.6).

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 authors did not state that they assessed validity.
Data extraction
Two reviewers extracted the data and a third reviewer resolved any discrepancies. Information on the method used to interpolate INR values between actual measurements was extracted from each study and classified as linear, halving or other.

The number enrolled in each study group, the proportion of time the group spent within the INR target range, and the group observation time were extracted. If the observation time was not reported for each group within a study, the proportion of patients in each group was multiplied by the total observation time.

Other data extracted for each study group included the type of anticoagulant, whether patients were self-monitored and the setting. The setting was classified as anticoagulation clinic, community practice or RCT. The anticoagulation clinic category included studies set in an anticoagulation or thrombosis clinic, and studies in which the physicians' role in patient care was limited to controlling INR levels. Self-monitored patient groups were classified as clinic-based if they were followed up by the clinic.

Methods of synthesis
How were the studies combined?
Individual anticoagulation treatment groups within each study were considered separately. The study groups were categorised according to the setting (RCT, clinic, community), publication date (1987 to 1997, 1998 to 2005), anticoagulant (warfarin, acenocoumarol, other), interpolation method (linear, other), study design (prospective, retrospective), and whether or not the patients were self-monitored. Within each category, the unadjusted mean percentage time spent in the therapeutic range was calculated as an incidence density with a 95% confidence interval (CI).

How were differences between studies investigated?
Meta-regression was used to investigate the association between study and group level factors (setting, publication date, anticoagulant drug, interpolation method, study design, self-management) and variation in anticoagulation control. Multiple linear mixed models were used and the analysis was weighted by the inverse variance of the proportion of time spent in the therapeutic range. The absolute increase or decrease in the percentage of time spent in the therapeutic range after adjusting for all other factors was reported with a 95% CI. Statistical significance appears to have been indicated by a p-value of less than 0.05.

Results of the review
Sixty-seven studies (42 prospective and 25 retrospective) were included in the review. These provided 123 study groups containing 50,208 patients.

The mean percentage of time spent in the therapeutic range across all study groups was 63.6% (95% CI: 61.6, 65.6).

The meta-regression showed the setting to have the greatest effect on anticoagulation control. The adjusted percentage of time spent in the therapeutic range in study groups from community practices was significantly less than in RCTs (-12%, 95% CI: -19.5, -4.8, p<0.0001) and anticoagulation clinics (-8.3%, 95% CI: -4.4, -12.1, p-value unclear). Self-monitoring groups spent a significantly higher percentage of time in the therapeutic range in comparison with non-self-managing groups (7%, 95% CI: 0.7, 13.3, p=0.03). There was no significant difference between warfarin and acenocoumarol, whereas the analysis of warfarin compared with other anticoagulants showed a significant improvement in effect in the other drugs category. No statistically significant effects were detected in the analyses of publication date, interpolation method or study design.

Authors' conclusions
Patients who have received anticoagulation therapy spend a significant proportion of time outside the INR therapeutic range. Patients from community practices showed worse anticoagulation control than those from anticoagulation clinics and clinical trials.

CRD commentary
The inclusion criteria were most fully described for the outcome of interest and relatively poorly described with regard...
to the participants, intervention and study design. The search for relevant studies appeared adequate, although it was incompletely reported and bias (language and publication) could have been introduced by limiting the review to studies published in English. The authors did not report methods to minimise bias when selecting studies for inclusion and study validity was not assessed. Rigorous methods seemed to have been used for the data extraction. The degree to which the study group characteristics used in the meta-regression analysis were pre-specified was unclear, although the review question appeared from the outset to be mainly concerned with the effect of study setting on the outcome. The analysis method did take account of residual heterogeneity and the potential lack of independence of INR control within studies.

Interpretation of the findings is, however, limited by the lack of information on patient characteristics in the study groups and the design, conduct and reliability of the results from the individual studies.

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

**Practice:** The authors stated that worse anticoagulation control in the community in comparison with RCTs has important implications for interpreting the results from RCTs and their applicability to practice.

**Research:** The authors stated that the relationship between measures of anticoagulation control and clinical outcomes requires further study. A population-based study without bias in participant selection and INR measurement was needed. Transferring processes of care used in anticoagulation clinics and RCTs to improve anticoagulation control in the community was an area that needs further work.

**Funding**
Institute for Safe Medication Practices Canada.

**Bibliographic details**

**PubMedID**
16685005

**DOI**
10.1378/chest.129.5.1155

**Original Paper URL**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Anticoagulants /therapeutic use; Blood Coagulation /drug effects; Confidence Intervals; Humans; Pulmonary Embolism /blood /prevention & control; Randomized Controlled Trials as Topic /methods; Treatment Outcome; Venous Thrombosis /blood /prevention & control

**AccessionNumber**
12006002462

**Date bibliographic record published**
31/05/2007

**Date abstract record published**
31/05/2007

**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.