Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review


CRD summary
This review concluded that in atrial fibrillation patients receiving orally administered anticoagulation, time in therapeutic range and percentage of international normalised ratio (INRs) in range effectively predicted INR control; time in therapeutic range accurately predicted reductions adverse events. The review was generally well conducted, but the lack of quality assessment of included studies limits the reliability of the authors’ conclusions.

Authors’ objectives
To determine the relationship between different outcome measures and adverse events in patients with atrial fibrillation receiving oral anticoagulation (vitamin-K antagonists).

Searching
MEDLINE, EMBASE and the Cochrane Library were searched from January 1990 to January 2008 for articles published in any language. Search terms were reported. Reference lists of retrieved trials and review articles were scanned.

Study selection
Randomised controlled trials (RCTs), prospective cohorts and retrospective studies of vitamin K antagonists in unselected adults with atrial fibrillation were eligible for inclusion. Studies had to report international normalised ratio (INR) control as a percentage of time in therapeutic range, percentage of INR in range, or similar measures. Studies had to enrol at least 25 patients and had a study duration or mean follow-up of at least three months.

The included studies examined vitamin K antagonist anticoagulants including warfarin. The mean age of participants ranged from 64 to 87 years. Study duration ranged from four to 42 months. Most of the studies were conducted in the USA and Europe (including 10 UK studies).

Two reviewers independently performed study selection.

Assessment of study quality
The authors assessed study blinding, but no formal validity assessment was reported.

Data extraction
Two reviewers independently extracted data on the incidence of time in therapeutic range, INR and adverse event rates. Disagreements were resolved by discussion. Studies with missing data were excluded from the analysis.

Methods of synthesis
Regression analysis was performed between INR control measures and adverse events.

Publication bias was estimated using funnel plot assessment, and Egger’s and Begg’s regression test.

Results of the review
Thirty-eight studies, with 47 study groups, were included in the review (>33,976 patients), including 15 RCTs, five prospective cohorts and 27 retrospective studies. The study sample size ranged from 25 to 6,454 patients. Thirty-six studies reported time in therapeutic range; 18 studies reported international normalised ratio (INR).

The time in therapeutic range ranged from 29 to 75% and was statistically significantly correlated with percentage of INRs in range (r=0.99, p<0.001). Compared with retrospective studies, RCTs had better INR control (65% versus 56%). The time in therapeutic range was statistically significantly negatively correlated with thromboembolic rates (r=-0.59) and major haemorrhage (r=-0.59). A 7% improvement in the time in therapeutic range would lead to
reduction of one haemorrhage per 100 patient years (retrospective studies only); a 12% improvement of time in therapeutic range would lead to reduction of one thromboembolic event per 100 patient years (retrospective studies only).

There was no evidence of publication bias.

**Authors' conclusions**
In atrial fibrillation patients that received orally administered anticoagulation, time in therapeutic range and percentage of INRs in range effectively predicted INR control and the time in therapeutic range accurately predicted reductions in adverse events.

**CRD commentary**
Inclusion criteria for the review were clearly defined. Several relevant databases were searched without language restrictions. Publication bias was assessed and was not detected. Attempts were made to reduce reviewer error and bias throughout the review process.

The authors did not state if quality assessment was undertaken, which made the reliability of trials difficult to determine. Trials were analysed using regression analysis; the effects of missing data were explored.

The review was generally well conducted, but the lack of quality assessment limits the reliability of the authors’ conclusions.

**Implications of the review for practice and research**
**Practice:** The authors stated that they have set a benchmark by which anticoagulation services can evaluate the impact of improving the percentage of time in therapeutic range in their patient cohort.

**Research:** The authors stated that the time in therapeutic range and percentage of INRs in range should both be reported and used as predictors in future studies of oral anticoagulation.

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