Effect of pharmacological therapies for stroke prevention on major gastrointestinal bleeding in patients with atrial fibrillation

CRD summary
This well-conducted review found that adjusted-dose vitamin K antagonists increased the risk of major gastrointestinal bleeding compared with placebo or aspirin when used for stroke prevention in atrial fibrillation patients; combining vitamin K antagonists with aspirin also increased this risk. The authors' findings are generally reliable but limited by the small number of trials and rarity of events.

Authors' objectives
To investigate the incidence of major gastrointestinal bleeding when using various antiplatelet and anticoagulant agents for stroke prevention in patients with atrial fibrillation.

Searching
MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to November 2010, limited to publications in English. Search terms were presented. A manual search of references in known articles was also conducted.

Study selection
Randomised controlled trials (RCTs) of adults with atrial fibrillation or flutter that compared oral pharmacological stroke prevention medications were eligible for inclusion. Eligible trials had to report the incidence of major gastrointestinal bleeding. Trials of patients with postoperative atrial fibrillation or valvular disease were excluded.

The included trials evaluated the following agents: aspirin, clopidogrel, dabigatran, triflusal, vitamin K antagonists (adjusted-dose or low-intensity), warfarin (adjusted-dose or low-intensity) and ximelagatran. There were five placebo or control arms, nine aspirin (or triflusal or indoprofen) arms, 17 vitamin K antagonists (14 adjusted-dose, three low-intensity arms), two arms for adjusted-dose vitamin K antagonists with aspirin (or triflusal), two arms for dabigatran and low-intensity vitamin K antagonists plus aspirin, one arm each for ximelagatran and clopidogrel plus aspirin. Five trials permitted off-protocol use of aspirin. All trials were conducted in the USA, Japan or Europe, but none in the UK. Mean ages of participants ranged from 65 to 75 years; the proportion of men ranged from 41% to 100%.

It appeared that two independent reviewers carried out the selection of studies.

Assessment of study quality
Trial quality was assessed using the Jadad scale with scores ranging from 0 to 5 points. A score of less than 3 was deemed to indicate low methodological quality.

Two independent reviewers carried out the quality assessment. Discrepancies between reviewers were resolved through discussion or by a third reviewer.

Data extraction
For each arm of each trial, the number of major gastrointestinal bleeding events and the person-years of follow-up were extracted, from which incidence rates of bleeding, with 95% confidence intervals, were calculated. Where available, data on incidence of minor gastrointestinal bleeding and of gastrointestinal ulcers were extracted.

Two reviewers independently extracted data.

Methods of synthesis
Trials were combined in meta-analyses using the Peto method with results presented as odds ratios (OR) with 95% confidence intervals. Separate meta-analyses were conducted for each pair-wise comparison of drugs for which data were available. Triflusal and indobufen were considered to be equivalent to aspirin as they all inhibit the...
cyclooxygenase-1 enzyme. Heterogeneity was assessed using $I^2$, with $I^2$ over 50% taken to indicate substantial heterogeneity.

Publication bias was assessed using Egger's test.

**Results of the review**

Sixteen trials were eligible for inclusion in the review. The trials included 42,983 patients (sample sizes ranging from 115 to 18,113) representing 93,131 person-years of follow-up. The median follow-up time was two years. One trial was of lower quality (Jadad score of 2); all others were of moderate or good quality (Jadad score of 3 or more).

The incidence rate of major gastrointestinal bleeding ranged from 0 to 8.9% per 1,000 person-years, or 0 to 1.4% if trials allowing off-protocol aspirin use were excluded.

Adjusted-dose vitamin K antagonist treatment was associated with a higher incidence of major gastrointestinal bleeding than placebo (OR 3.21, 95% CI 1.32 to 7.82; four trials) or aspirin (OR 1.92, 95% CI 1.08 to 3.41; seven trials).

Adjusted-dose vitamin K antagonist plus aspirin was associated with a higher incidence of bleeding than vitamin K antagonists alone (OR 2.66, 95% CI 1.05 to 6.74; two trials) or aspirin alone (OR 4.72, 95% CI 1.35 to 16.49; one trial).

Aspirin was associated with a higher incidence of bleeding than placebo but the result was not statistically significant (OR 3.23, 95% CI 0.56 to 18.66; three trials).

Dabigatran was found to be worse (increased chance of bleeding) than adjusted-dose vitamin K antagonists (OR 1.30, 95% CI 1.06 to 1.59) and aspirin plus clopidogrel worse than aspirin alone (OR 1.93, 95% CI 1.46 to 2.56), but these results were both based on one trial.

No other significant relationships were found in the other six drug comparisons considered.

Only one analysis had substantial heterogeneity ($I^2>50$%).

No evidence of publication bias was identified.

**Authors' conclusions**

Major gastrointestinal bleeding was a significant concern in stroke prevention. Adjusted-dose vitamin K antagonists and dabigatran gave the greatest risk of major gastrointestinal bleeding. Therapies using two agents in combination also increased risk. Aspirin was not associated with an increased risk, but this may have been due to the small sample size.

**CRD commentary**

This review was generally well conducted. Inclusion criteria for the review were explicitly stated. Relevant sources were searched for studies. Quality assessment was undertaken using a standard checklist and trials were generally of moderate to good quality. There was no evidence of publication bias or of substantial heterogeneity across trials.

The authors acknowledged some limitations in the analysis, particularly that there were generally few trials for any specified drug comparison and that sample sizes and numbers of events were small, which limited the ability of the analysis to detect differences between treatments. Combining triflusal and indobufen with aspirin may have been inappropriate as these are not exactly the same treatment. The inclusion of trials allowing off-protocol aspirin use may have affected the results by raising incidence of major gastrointestinal bleeding in patients who received aspirin. The trials contained relatively few elderly people, so the generalisability of these results to the general population with atrial fibrillation was uncertain.

Despite these limitations, the authors' findings are likely to be reliable, and their recommendation that future trials in stroke prevention should report data on major gastrointestinal bleeding is appropriate.

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

**Practice:** The authors made no recommendations for clinical practice.
Research: The authors stated that future trials of pharmacological stroke prevention should make greater effort to report incidence of major gastrointestinal bleeding.

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