Meta-analysis of randomised controlled trials of the effectiveness of antiarrhythmic agents at promoting sinus rhythm in patients with atrial fibrillation


Authors' objectives
To assess the effectiveness of anti-arrhythmic drugs at promoting sinus rhythm in patients with atrial fibrillation by conducting a meta-analysis of randomised controlled trials (RCTs).

Searching
MEDLINE was searched for trials for which results were available by August 2001; the search terms were reported. The bibliographies of relevant articles were examined. Only articles published in the English language were sought. Unpublished studies and abstracts were not excluded.

Study selection
Study designs of evaluations included in the review
Only RCTs were included.

Specific interventions included in the review
Only studies evaluating anti-arrhythmic agents were included. Studies using anti-arrhythmic agents for prophylaxis of atrial fibrillation alone were excluded. The agents used in the included studies were class I drugs (further classified into class IA and IC), class II drugs, class III drugs, class IV drugs and digoxin (12 studies).

Participants included in the review
Studies of patients with atrial fibrillation were eligible for inclusion. Studies that enrolled patients with induced atrial fibrillation were excluded.

Outcomes assessed in the review
Only studies reporting the proportion of patients in sinus rhythm at follow-up were included. Studies that followed patients for less than 60 minutes after drug administration were excluded. The primary outcomes of interest in the review were the proportion of patients in sinus rhythm at follow-up and mortality. The median duration of follow-up for the included studies was one day (range: 0.04 to 1,096; mean 46, standard deviation 136).

How were decisions on the relevance of primary studies made?
The studies were independently assessed for relevance by more than one reviewer (the number of reviewers was unclear) and any disagreements were resolved by consensus.

Assessment of study quality
The studies were quality assessed, according to the Jadad validity assessment tool, for randomisation, blinding, and withdrawal and drop-out. Allocation concealment was also assessed. The studies were scored out of seven points. The studies were independently assessed for quality by more than one reviewer (the number of reviewers was unclear) and any disagreements were resolved by consensus.

Data extraction
Data were extracted independently by two reviewers and checked for accuracy after data entry. For the two outcomes of interest, the proportion of participants with the outcome at follow-up in the treatment and control groups, and the difference in proportions (treatment difference) were extracted. Data from the original studies are available on the Heart website (www.heartjnl.com), but access to this information is only free to subscribers.
Methods of synthesis
How were the studies combined?
The studies were combined in a repeated measures random-effects model. The five classes of drugs were compared on the two outcome measures. The inverse variance of the outcome measure estimate was used to weight the outcome measure at each time point. Least-square means and their 95% confidence interval (CIs) for the treatment difference were derived from the models at the median follow-up duration.

How were differences between studies investigated?
Three sensitivity analyses were carried out on the sinus rhythm outcome variable: subgroup analyses were used to compare studies reporting a follow-up of less than one week to trials with at least one week follow-up, and also to compare use of the drug intervention for conversion to as opposed to maintenance of sinus rhythm; the effects of using different study cohorts was assessed (further details provided in the paper); and the effect of study quality on the model was assessed. The latter two analyses were also carried out on the mortality data, in addition to an analysis based on the assumption that there was no death in studies not reporting mortality.

The effect of the class III drug amiodarone compared to any other anti-arrhythmic agent was assessed. The effect of including one large trial, which had a slightly different population from all the other studies, was also considered.

Results of the review
Ninety-one RCTs (n=8,563) were included.

Effect of anti-arrhythmic agents on sinus rhythm.
Class IA, IC and III drugs were associated with significant increases in the proportion of patients in sinus rhythm compared with placebo. In addition, the class IC drugs were associated with a significant increase in the proportion of patients in sinus rhythm compared with class IV drugs.

Compared with placebo, the mean treatment difference was 21.5% (95% CI: 16.3, 26.8, p<0.0001) for class IA drugs (7 trials), 33.1% (95% CI: 23.3, 42.9, p<0.0001) for class IC (17 trials), 17.4% (95% CI: 11.5, 23.3, p=0.001) for class III (19 trials), and 13.1% (95% CI: -7.2, 33.3, p=0.15) for digoxin (4 trials).

The mean treatment difference was 4.1% (95% CI: -8.0, 16.2, p=0.42) for class IA versus class III drugs (6 trials), -3.4% (95% CI: 17.2, 10.5, p=0.6) for class IC versus class III (10 trials), 43.2% (95% CI: 11.5, 75.0, p=0.03) for class IC versus class IV (4 trials), and 15.2% (95% CI: -43.7, 74.2, p=0.19) for class III versus digoxin (2 trials). There appears to be an error in the result for class IC versus class III drugs since the mean treatment difference (-3.4%) lies outside the confidence range reported (95% CI: 17.2, 10.5).

Effect of anti-arrhythmic agents on mortality.
There was no significant difference in mortality between active treatment and placebo, or between active treatment and comparison drug, for any of the classes of anti-arrhythmic drugs considered.

Compared with placebo, the mean treatment difference was 0.96% (95% CI: -0.45, 2.36, p<0.14) for class IA drugs (5 trials), -0.08% (95% CI: -0.20, 0.04, p=0.16) for class IC (14 trials), -0.11% (95% CI: -0.32, 0.09, p=0.25) for class III (17 trials), and 0.02% (95% CI: -0.01, 0.06, p=0.12) for digoxin (4 trials).

The mean treatment difference was 0.17% (95% CI: -0.58, 0.92, p=0.53) for class IA versus class III drugs (5 trials), -0.26% (95% CI: -1.10, 0.59, p=0.50) for class IC versus class III (8 trials), -0.06% (95% CI: -2.26, 2.13, p=0.91) for class IC versus class IV (4 trials), and 0.48% (95% CI: -13.71, 14.67, p=0.74) for class III versus digoxin (2 trials).

The authors also reported the data for the individual class IA, IC and III drugs.

Sensitivity analyses.
In comparison with placebo, there was an association between anti-arrhythmic drugs and increased sinus rhythm.
among the trials of class IC and class III drugs that followed patients up for less than 7 days. There was also an association between anti-arrhythmic drugs and increased sinus rhythm, compared with placebo, among the trials of class IA and class III drugs. When the large trial was included in the analysis, the results remained non significant. Also, the results were not altered when the analysis was adjusted for study quality or study cohorts. The results relating to mortality were not altered for any of the sensitivity analyses.

Authors' conclusions
Class IA, IC and III anti-arrhythmic drugs are associated with increased sinus rhythm in comparison with placebo, while class IC drugs are associated with increased sinus compared with class IV drugs. It is unclear whether any drug class is associated with increased or decreased mortality.

CRD commentary
The review question was clear in terms of the intervention, outcomes and study design. However, the eligibility criteria for the participants was limited. Only one electronic database was searched, unpublished data were excluded and language restrictions were applied. Therefore, it is possible that studies were missed. The study selection, data extraction and validity assessment processes were carried out by more than one reviewer, which helps to reduce errors and bias. Details about the included studies were made available on the journal website, although access is only free to subscribers. However, apart from age and gender, no participant details are available. Given the very broad inclusion criteria for participants, it would have been useful to have information on the disease characteristics of the participants on which to assess the clinical heterogeneity of the population. The authors note that the treatment effectiveness estimates should be interpreted with caution due to the wide variety of drug classes considered and differences in the duration of follow-up. Sensitivity analyses were carried out for some factors, but there was limited consideration of the possibility of heterogeneity within each class of drugs. The analysis of the impact of length of follow-up had limitations and there is no a priori justification given for choosing a cut-off point of one week. While the authors' conclusions appear to follow from the results presented, conclusions cannot be drawn about the effectiveness of specific drugs.

Implications of the review for practice and research
Practice: The authors state that the impact of each class of drug on sinus rhythm, mortality, quality of life and patient compliance should be considered by patients, physicians and policy makers.

Research: The authors state that there is a need for appropriately powered studies comparing specific class III drugs.

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