Benefits and risks of long-term amiodarone therapy for persistent atrial fibrillation: a meta-analysis

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CRD summary
This meta-analysis assessed the efficacy and safety of amiodarone compared with placebo or rate-control drugs for treating persistent atrial fibrillation, in terms of mortality, rhythm control, withdrawal from treatment, and hospitalisation. The authors concluded that amiodarone was safe and effective, but some patients might be unable to tolerate it. These conclusions appear to be broadly reliable.

Authors’ objectives
To assess the effectiveness and safety of amiodarone, compared with a placebo or rate-control drug, in achieving sinus rhythm in patients with atrial fibrillation persisting for more than 30 days.

Searching
MEDLINE (1966 to 2008), EMBASE (1988 to 2008), and the Cochrane Central Register of Controlled Trials (CENTRAL; 2008, Issue 2) were searched, with no language restrictions. The search terms were reported and the reference lists of retrieved papers were reviewed. There was no apparent attempt to contact experts or retrieve unpublished trials.

Study selection
Randomised controlled trials that compared amiodarone with a placebo or a rate-control drug, in the treatment of atrial fibrillation persisting for more than 30 days, in adult patients, were eligible for inclusion. Trials that evaluated the effects of amiodarone on atrial fibrillation persisting for less than 30 days, or compared amiodarone with another rhythm control antiarrhythmic drug, were excluded. Trials of patients with any condition that meant amiodarone should not be given were excluded.

The included trials evaluated various regimens of amiodarone. The primary outcome was mortality from any cause. The secondary outcomes were: rhythm control at the end of the trial period, withdrawals from the trial, and hospitalisations associated with the intervention. All the trials used an echocardiogram to measure the heart rhythm at follow-up appointments.

Two reviewers independently applied the inclusion criteria and there were no disagreements.

Assessment of study quality
The quality of the included trials was assessed using the Cochrane Collaboration criteria for quality assessment. Randomisation, allocation concealment, and blinded outcome assessment were judged as adequate, inadequate, or unclear. The details of how the individual components were assessed were not reported. The number of participants lost to follow-up in each trial was reported. Some authors were contacted for clarification or for additional data.

Two reviewers independently assessed the quality of the included trials and there were no discrepancies between them.

Data extraction
Two reviewers independently extracted the incidence data per patient per year and calculated relative risks, with 95% confidence intervals. There were no disagreements between the reviewers.

Methods of synthesis
The effect of amiodarone was reported as the relative risk and 95% confidence interval, using a random-effects model. Heterogeneity between trials was assessed by the $\chi^2$ and $I^2$ statistics and a fixed-effect model was used when no heterogeneity was found. Publication bias was assessed by a funnel plot. Sensitivity analysis was performed to
determine whether the results were robust.

**Results of the review**

Twelve trials (n=5,060 participants) from nine countries met the inclusion criteria and they were all published in English. Eight trials compared amiodarone with a rate-control drug and four trials compared it with a placebo. Concealment of allocation was adequate in eight trials, inadequate in one trial, and unclear in two trials. Six trials were double blind, two were single blind, and in four trials the outcome assessment was not blind. All the trials reported an intention-to-treat analysis.

Where reported, the duration of follow-up ranged from six to 60 months. There was statistically significant heterogeneity between trials for all secondary outcomes and the funnel plot showed the possible presence of publication bias.

There was no statistically significant difference between amiodarone and placebo or a rate control drug, in long-term mortality: 4.7 versus 3.9 per 100 patient-years (12 trials, n=5,060); one trial received a weight of 71.46%. Amiodarone was more effective compared with placebo or a rate control drug in achieving sinus rhythm: 21.3 versus 9.2 per 100 patient-years (RR 3.2, 95% CI 1.9 to 5.5; 11 trials, n=5,044). The incidence of hospitalisation did not increase with amiodarone treatment compared with placebo or a rate control drug (five trials, n=2,932).

The risk of withdrawal from the trial was significantly greater in the amiodarone group compared with placebo or a rate control drug: 10.7 versus 1.9 per 100 patient-years (RR 3.0, 95% CI 1.4 to 6.2; nine trials, n=3,176). These findings did not change in any of the sensitivity analyses.

**Authors’ conclusions**

Amiodarone appeared to be effective and safe for the long-term treatment of patients with persistent atrial fibrillation, but some patients withdrew because they could not tolerate the adverse effects. The evidence for low-dose regimes of 100mg per day was inconclusive as there were not enough data.

**CRD commentary**

This review addressed a well-defined question in terms of participants, interventions, outcomes, and study design. The search included appropriate electronic databases, but no attempts were made to retrieve unpublished studies and all the relevant data might not have been included. To minimise bias and errors during the review process, two reviewers independently selected trials, extracted data, and assessed the quality of the included trials. The characteristics of the individual trials were presented. Validity was assessed using the Cochrane criteria for quality. Potential sources of heterogeneity were explored and reported. Sensitivity analysis demonstrated that the results were robust to changes in the factors considered.

The authors’ conclusions were consistent with the evidence shown and are likely to be reliable.

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

**Practice:** Long-term amiodarone therapy appeared to be effective and safe for the treatment of persistent atrial fibrillation, but significant withdrawal from the trials raised concern.

**Research:** There was a need for research comparing amiodarone with new analogues, such as dronedarone.

**Funding**

No grants or awards received from pharmaceutical companies or other private companies.

**Bibliographic details**

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.