Amiodarone prophylaxis for atrial fibrillation after cardiac surgery: meta-analysis of dose response and timing of initiation

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CRD summary
This review concluded that total amiodarone doses of 3,000 mg or higher may be more effective than lower doses in reducing the rate of post-operative atrial fibrillation after cardiac surgery. Pre-operative initiation of amiodarone appears to be unnecessary. Given the potential weaknesses in the review methods and analyses, it is difficult to assess the robustness of the authors' conclusions.

Authors' objectives
To assess optimal dosing regimens of prophylactic amiodarone for reducing the incidence of atrial fibrillation (AF) after cardiac surgery, and to assess whether pre- or post-operative initiation of amiodarone is superior.

Searching
MEDLINE, EMBASE and the Cochrane CENTRAL Register were searched for studies published between 1966 and December 2005; the key terms were reported. The reference lists of retrieved studies were also checked for additional studies. Only English language studies were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies assessing prophylactic amiodarone for AF after cardiac surgery were eligible for inclusion, providing that the dose and timing of the initiation therapy were reported. In the included studies, amiodarone prophylaxis was either initiated pre-operatively and continued post-operatively (6 studies) or initiated during or after cardiac surgery (8 studies). The duration of amiodarone prophylaxis ranged from 3 to 32 days. The total oral-equivalent amiodarone dose ranged from 960 to 11,102 mg. The majority of trials compared the intervention with placebo; one used a magnesium or placebo comparison and another used pacing or placebo.

Participants included in the review
The inclusion criteria were not specified in terms of participants, but it was clear that studies of patients undergoing cardiac surgery for AF were eligible for inclusion. Definitions of arrhythmia varied and were reported in the review. The type of cardiac surgery used in the included studies was either coronary artery bypass graft (CABG) (9 studies) or CABG and/or valve replacement (5 studies). Most of the patients were men (no data reported). The mean age and standard deviation for both the amiodarone and control groups was the same (63 +/- 4 years).

Outcomes assessed in the review
Studies were eligible for inclusion if they reported the incidence of AF.

How were decisions on the relevance of primary studies made?
One reviewer selected the studies for inclusion and a second checked the decisions.

Assessment of study quality
The validity of the included studies was assessed by evaluating the potential for methodological bias. The studies were rated on methods and results reported relating to intention-to-treat analysis, blinding procedures, concealment of allocation, equivalence of groups at baseline, adherence to treatment protocol and independence from drug
manufacturer influence. There was a possible maximum rating of 45 points. Each item was rated as 10 points, except for independence from drug manufacturer which was rated as 5. The validity and reliability of the validity assessment tool were tested. It is not clear how many reviewers performed the assessment.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

**Methods of synthesis**

How were the studies combined?
The studies were pooled in a meta-analysis. A forest plot using pooled ORs was constructed to determine the effect of dose on the incidence of AF, subdivided into low dose (<3,000 mg), medium dose (3,000 to 5,000 mg) and high dose (>5,000 mg). A second forest plot was constructed to compare studies of prophylactic treatment with amiodarone initiated pre-operatively and post-operatively. Publication bias was assessed using funnel plots.

How were differences between studies investigated?
Statistical heterogeneity was investigated using the Q statistic. Subgroup analyses were used to assess the effects of study validity: studies with more potential for bias (internal validity scores less than the median) were compared with studies with less potential for bias (internal validity scores greater than the median).

**Results of the review**

Fourteen RCTs (n=2,864) were included.

Eleven of the 14 RCTs were double-blind, but only four concealed allocation. Six studies included intention-to-treat analyses. Four studies were funded by foundations or public sources and three were partially funded by pharmaceutical manufacturers. Scores for the internal validity assessment ranged from 14 (31%) to 38 (94%), with a mean of 24.4 (54%), out of a possible score of 45. Studies that had less potential for bias demonstrated a slightly greater drug effect than those with more potential, although the difference was not statistically significant. Trials with more potential for bias appeared to contain more error variance, but the pooled findings did not appear to be biased by the study methods.

**Post-operative AF.**

Amiodarone reduced the incidence of AF by 51% in comparison with placebo (OR 0.49, 95% CI: 0.41, 0.59, p<0.001).

Differences in the odds of developing AF post-operatively were not statistically significant between the low-, medium- and high-dose groups: OR 0.58 (95% CI: 0.44, 0.77) for the low-dose group (<3,000 mg; 6 studies), 0.45 (95% CI: 0.30, 0.69) for the medium-dose group (3,000 to 5,000 mg; 4 studies) and 0.44 (95% CI: 0.33, 0.58) for the high-dose group (>5,000 mg; 4 trials).

**Pre- versus post-operative initiation of amiodarone.**

There were no significant differences in patients in whom amiodarone prophylaxis was initiated pre-operatively and continued post-operatively (6 studies) compared with those in whom amiodarone prophylaxis was initiated post-operatively (8 studies), OR 0.50 (95% CI: 0.39, 0.63) and OR 0.48 (95% CI: 0.37, 0.63), respectively (p=0.862).

Heterogeneity amongst all the included trials was not significant. The funnel plot showed no evidence of publication bias.

**Authors’ conclusions**

Total amiodarone doses of 3,000 mg or higher may be more effective than lower doses at reducing the rate of post-operative AF after cardiac surgery. Pre-operative initiation of amiodarone does not appear to be necessary.
CRD commentary
This review answered a clear research question, but some studies might have been missed through the exclusion of studies not published in English and the apparent lack of searches for unpublished material. Funnel plots were used to assess the risk of publication bias, but the reliability of these tests is unclear given the number of included studies. Some attempts were made to reduce reviewer error and bias when selecting the studies and extracting the data, though it is unclear whether similar steps were taken during the assessment of study validity. Study validity was assessed and the reliability of the assessment instrument investigated. The effects of variable study quality were also investigated further in subgroup analyses, though the statistical methods used were not reported (i.e. fixed-effect versus random-effects models).

Statistical heterogeneity was assessed but the authors reported few details of the types of included participants, which makes it difficult to assess the level of clinical heterogeneity between the studies. However, it does appear that the studies differed in terms of some characteristics, such as the definition of arrhythmia. Assumptions were also made when estimating the equivalent oral doses of amiodarone, which could have introduced bias. Comparisons of pre- and post-operative amiodarone were not made using direct methods, which raises questions with regard to their reliability. Overall, it is difficult to assess the reliability of the review's conclusions, given the potential weaknesses in the review methods and analyses.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further prospective randomised trials are needed to determine the optimal dose and time of initiation (pre- versus post-operative) of amiodarone, for the prevention of AF after cardiac surgery.

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