Amiodarone prophylaxis reduces major cardiovascular morbidity and length of stay after cardiac surgery: a meta-analysis
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CRD summary
The authors assessed the use of prophylactic amiodarone given around the time of cardiac surgery. They found that the incidence of atrial fibrillation or flutter, ventricular tachycardia or fibrillation, and stroke were reduced by amiodarone. Length of hospital stay was also reduced, but there was no difference in death rates. The review was well conducted and the results appear reliable.

Authors' objectives
To assess whether prophylactic amiodarone decreases the incidence of major cardiovascular morbidity, length of hospital stay and mortality after cardiac surgery.

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane CENTRAL Register were searched from the earliest possible dates to February 2005; the search terms were given. Both English and non-English language papers were sought. The bibliographies of published reviews were also checked. Unpublished studies were not eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Double-blind, randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing amiodarone with placebo were eligible for inclusion. Where stated, the total amiodarone dose in the included studies ranged from 2.0 to 7.5 g. The method of administration was either oral or intravenous, with administration initiated before, during or immediately after surgery, and continued post-operatively for between 24 hours and 7 days. Details of the dosing regimens were given in the paper. One study was excluded because the amiodarone regimen differed markedly from those in other studies. Between 26 and 89% of the included participants were also taking prophylactic beta-blockers. The duration of cardiopulmonary bypass ranged from 56 to 153 minutes.

Participants included in the review
Studies of people undergoing coronary artery bypass grafting and/or valve surgery were eligible for inclusion. In the included studies, between 65 and 86% of the participants were men and the mean ages ranged from 59 to 73 years. The proportion of participants with a history of supraventricular tachycardia ranged from 0 to 10%. Between 16 and 53% had a history of myocardial infarction (MI), 38 to 73% hypertension, and 7.5 to 33% diabetes.

Outcomes assessed in the review
To be eligible for inclusion, the primary studies had to evaluate the occurrence of atrial fibrillation, atrial flutter or supraventricular tachycardia as a primary outcome. The other outcomes of interest for the review were the incidences of ventricular tachycardia or fibrillation, stroke, MI and death, and the length of hospital stay. Adverse events were also reported. The outcomes were assessed during hospitalisation or at 30 days post-operatively.

How were decisions on the relevance of primary studies made?
One author screened the results of the searches. Three authors read all retrieved papers and decided upon inclusion.

Assessment of study quality
The authors said that, as part of the inclusion criteria, only studies that clearly described drug administration, co-
morbid conditions, risk profiles of participants, study design and methods were eligible for inclusion. Studies were also assessed on the basis of methods of randomisation and completeness of follow-up. Quality was assessed, but the authors did not state how many reviewers performed the assessment.

**Data extraction**
Two authors independently extracted all of the data using a standardised form. Any discrepancies were resolved by consensus between all authors. Relative risks (RRs) were calculated for those outcomes in the included studies that could be treated as dichotomous variables. Weighted mean differences (WMDs) were calculated for length of hospital stay in those studies where the mean and standard deviation were specified.

**Methods of synthesis**
How were the studies combined?
The data were pooled using the random-effects model of DerSimonian and Laird. Pooled RRs were calculated for dichotomous outcomes and WMDs for length of hospital stay, along with associated confidence intervals (CIs). A funnel plot was used to check for publication bias.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the I-squared measure. Subgroup analyses were performed according to timing of the initial administration of amiodarone (or placebo). These were categorised as pre-operative if the drug was started before surgery, and peri-operative if started during or immediately after surgery. Comparisons were made between studies that administered oral amiodarone alone or intravenous amiodarone alone.

**Results of the review**
Ten RCTs (1,744 participants) were included.

Amiodarone decreased the incidence of atrial fibrillation or flutter (RR 0.64, 95% CI: 0.55, 0.75, P<0.001). This decrease was similar for both pre-operative and peri-operative treatment, and for oral and intravenous administration.

Amiodarone also decreased the incidence of ventricular tachycardia or fibrillation (RR 0.42, 95% CI: 0.28, 0.63, P<0.001). The results were similar when studies that did not differentiate between sustained and nonsustained ventricular tachycardia or fibrillation were removed (RR 0.34, 95% CI: 0.18, 0.66).

Amiodarone reduced the incidence of stroke (RR 0.39, 95% CI: 0.21, 0.76, P=0.005) and the length of hospital stay (WMD -0.63 days, 95% CI: -1.03, -0.23, P=0.002). No statistically significant differences in mortality were seen between the two treatment groups (RR 0.84, 95% CI: 0.43, 1.65), or in the incidence of MI (RR 0.71, 95% CI: 0.31, 1.62). There was no evidence of statistical heterogeneity or publication bias, although the latter could not be assessed for the outcome of mortality. Three studies found significantly more adverse events in the amiodarone groups (nausea, bradycardia and increased intensive care monitoring or support).

**Authors' conclusions**
Amiodarone decreases the incidence of atrial fibrillation, ventricular tachyarrhythmias, and stroke and length of hospital stay after cardiac surgery.

**CRD commentary**
The aims and inclusion criteria for this review were clearly stated. Searches of several relevant databases were performed. However, unpublished studies were excluded. It is possible that studies were missed, although the authors tested for publication bias. The methods of the review were appropriate and the quality of the included studies was assessed. Information on the study designs and participants was clear, with additional material stated as being available on the Annals of Internal Medicine website (although a subscription to the journal may be required for access). Heterogeneity was considered and the meta-analysis was appropriate. The authors commented that the
effectiveness of beta-blockers as prophylaxis is proven. However, since their use was not uniform within the studies, it is possible that this could have had some effect on the results. This was a well-conducted review and the data presented support the authors' conclusions.

Implications of the review for practice and research
Practice: The authors stated that patients undergoing open-heart surgery should receive prophylaxis with a beta-blocker, unless contraindicated, in accordance with current guidelines. The value of routine use of additional amiodarone remains uncertain.

Research: The authors stated that a large multicentre RCT is needed to further evaluate the prophylactic use of amiodarone in people already receiving beta-blocker prophylaxis, to assess any additional benefit.

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