Quantitative overview of randomized trials of amiodarone to prevent sudden cardiac death

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Authors' objectives
To assess the effect of amiodarone on mortality, and the impact of differences in patient population and study design on trial outcomes.

Searching
MEDLINE and BIOSIS Previews were searched for all trials of amiodarone published between January 1985 and March 1997. The references of the retrieved articles and relevant conference proceedings were also examined. Professionals were contacted for additional trials.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with at least 3 months treatment and follow-up were included.

Specific interventions included in the review
Amiodarone in doses ranging from 200 to 400 mg/day. Amiodarone was compared with placebo, usual care, or active controls such as propranolol, sotalol and individualised treatment with predominantly type I anti-arrhythmic agents.

Participants included in the review
Patients at risk of sudden cardiac death. These included patients with coronary artery disease, clinical congestive heart failure, prior myocardial infarction and documented arrhythmia.

Outcomes assessed in the review
Total mortality, cardiac death and sudden death were assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not state that they assessed quality.

Data extraction
Studies were abstracted by two independent reviewers and were checked by a third, with any differences being resolved by consensus. Only data reported on an intention to treat basis were analysed.

Methods of synthesis
How were the studies combined?
The odds ratios (ORs) were combined using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.1) to yield overall and subgroup summary estimates.

How were differences between studies investigated?
Subgroup analyses were carried out a priori based on the following:

- the primary patient population (post-myocardial infarction, left ventricular dysfunction or post-cardiac arrest);
whether the patient inclusion criteria required documentation of a minimum number of ventricular premature beats per hour on a 24-hour Holter recording; and

the type of control (placebo, usual care or active anti-arrhythmic).

The hierarchical Bayes linear model (see Other Publications of Related Interest no.2) was used to determine whether subgroups of trials had results that were systematically different from the others.

Results of the review
Fifteen RCTs with a total of 5,864 patients (2,936 to amiodarone and 2,928 to control) were included.

The OR for total mortality in amiodarone-treated patients versus control was 0.81 (95% confidence interval, CI: 0.69, 0.94, p<0.01). The OR was 0.77 (95% CI: 0.66, 0.89, p<0.001) for cardiac mortality, 0.70 (95% CI: 0.58, 0.85, p<0.001) for sudden death, and 1.15 (95% CI: 0.85, 1.56, p=0.37) for non-cardiac death.

In the subgroup analyses total mortality, cardiac mortality and sudden death were reduced to a similar degree in each category of patients (post-myocardial infarction, left ventricular dysfunction and post-cardiac arrest). There was a trend towards greater risk reduction in trials requiring evidence of arrhythmia than in the remaining trials.

The OR for total mortality was lower in trials with usual care controls (OR 0.58, 95% CI: 0.41, 0.83, p=0.003) and active controls (OR 0.73, 95% CI: 0.43, 1.25, p=0.25), than in those with placebo controls (OR 0.90, 95% CI: 0.76, 1.06, p=0.20).

Authors' conclusions
Amiodarone reduced total mortality by 10 to 19% in patients at risk of sudden cardiac death. Amiodarone reduced risk similarly in patients after myocardial infarction, with heart failure, or with clinically evident arrhythmia. The apparent inconsistencies among the results from the RCTs appear to have been due to the small sample sizes and the type of control group used, and not the type of patient enrolled.

CRD commentary
This was a well-presented review which gave adequate details of the studies included and the statistical techniques used. However, there was no information on how the studies were selected for inclusion or whether the included studies were quality assessed. It was unclear whether attempts to search for foreign language literature were made. The authors were rigorous in their attempts to assess heterogeneity between the studies.

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Other publications of related interest
JE. Bayes method for combining the results of cancer studies in humans and other species. JASA 1983;78:293-308.


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