Amiodarone for the prevention of sudden cardiac death: a meta-analysis of randomized controlled trials

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CRD summary
This review concluded that for people at risk of sudden cardiac death (post-myocardial infarction or with heart failure) amiodarone reduced cardiac and cardiovascular death, but not overall mortality. Although there were adverse effects and the discontinuation rate was relatively high, amiodarone should be considered for people not eligible for cardioverter defibrillators. Overall the review was well-conducted and conclusions appear reliable.

Authors' objectives
To assess the efficacy and safety of amiodarone in preventing sudden death.

Searching
MEDLINE (1966 to 2007) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Search terms were provided. US Food and Drug Administration and clinicaltrials.gov websites checked. The search was limited to studies published in English. Bibliographies of relevant reviews were checked.

Study selection
Randomised controlled trials (RCTs) that assessed the effects of amiodarone in preventing sudden death were eligible for inclusion if they had treatment of more than 30 days and follow-up of six months or longer. The comparator group had to be placebo or inactive control. Studies had to report all-cause mortality. Studies on people with shock refractory ventricular arrhythmias and out-of-hospital cardiac arrest or in people under 18 years old were excluded. Studies of people with implantable cardioverter defibrillators were excluded (unless included in both study arms). Outcomes of interest were sudden cardiac death, cardiovascular death and all-cause mortality. Safety endpoints were study drug discontinuation, pulmonary toxicity, thyroid toxicity, elevation of alanine aminotransferase, aspartate aminotransferases and symptomatic bradycardia.

Inclusion criteria for participants in individual studies were acute myocardial infarction, heart failure, frequent premature ventricular contractions, non-sustained ventricular tachycardia, cardiomegaly, resuscitated cardiac arrest, sustained ventricular tachycardia/ventricular fibrillation (VT/VF) with ejection fraction less than 40%, inducible VT/VF with ejection fraction less than 40%, or syncope. Four studies included people with myocardial infarction. Seven studies included those with heart failure. In others, where reported, between 39% and 80% of patients had prior myocardial infarction and 18% to 52% had heart failure; mean ejection fraction ranged from 18% to 44%. Mean ages ranged from 57 to 68 years. Between 68% and 99% were men.

Amiodarone dose ranged from 200mg/day to 400mg/day; most studies used 200mg/day. Where reported, between 4% and 100% were also on beta blockers and 31% to 90% were on angiotensin converting enzyme (ACE) inhibitors.

Studies were assessed for inclusion by two reviewers independently.

Assessment of study quality
Study quality was assessed using the Delphi Consensus Criteria. The maximum score was 9. Scores of 6 or more were considered high quality.

Quality appeared to have been assessed by two reviewers independently.

Data extraction
In the study where implantable cardioverter defibrillators were used, the incidence of implantable cardioverter defibrillators discharges were included in the sudden cardiac death outcome.
The numbers of events were extracted and odds ratio (OR) and 95% confidence intervals (CI) calculated. Data were extracted by two reviewers independently.

**Methods of synthesis**
Outcomes were analysed on an intention-to-treat basis. The total numbers and percentages of events were calculated. Pooled OR and 95% CI were calculated using a fixed-effect and a random-effects model. Results for the random-effects model were reported. Numbers need to treat were calculated.

Heterogeneity was assessed using Cochran's Q statistic. Sensitivity analyses that excluded individual trials one at a time were performed. Subgroup analyses were conducted based on amiodarone dosage (up to 200mg per day and >200mg per day), study population (post myocardial infarction, heart failure), aetiology of cardiomyopathy (ischaemic, non-ischaemic), concomitant beta-blocker use (<50% and 50% or more) and follow-up duration (12 months or more and <12 months).

A funnel plot was used to assess publication bias.

**Results of the review**
Fifteen RCTs (8,522 participants) were included: 10 (7,151 participants) placebo controlled (eight double blind and two single blind); and five (1,371 participants) open label inactive control studies. Study size varied between 34 and 2,521 participants. Follow-up ranged from 12 to 45 months. Twelve studies were considered good quality (scored 6 or more). Studies were published between 1987 and 2006.

There was no evidence of publication bias.

There was no evidence of heterogeneity for any analysis.

Compared to control, amiodarone significantly reduced the incidence of sudden cardiac death (7.2% versus 9.7%, OR 0.72, 95% CI 0.61 to 0.84, p<0.001) and cardiovascular death (14.0% versus 16.3%, OR 0.82, 95% CI 0.71 to 0.94, p=0.004). There was some reduction in all-cause mortality, but this did not reach statistical significance (18.1% versus 19.6%, p=0.093). There was no difference in deaths due to heart failure.

Sensitivity analysis results were similar when the largest trial was removed (see paper for details).

Subgroup analyses revealed no significant differences in results for sudden cardiac death, cardiovascular death or all-cause mortality (see paper for details).

End-organ toxicities were more common with amiodarone compared to control: pulmonary 2.9% versus 1.5%; thyroid 3.6% versus 0.4%, p<0.001; hepatic 1.85% versus 0.70%, p=0.015. Bradyarrhythmias (2.8% versus 1.5%, p=0.008) and cancer deaths were also more common (0.7% versus 0.02%, p=0.0501; four trials).

The percentage of those assigned to amiodarone who discontinued treatment was 28.7. In trials that reported discontinuation in placebo groups, the rate was higher for amiodarone than placebo (31.6% versus 21.1%, p<0.0001; nine trials).

**Authors' conclusions**
In people with cardiomyopathy, amiodarone reduced the risk of sudden cardiac death by 26% and cardiovascular death by 18%; overall mortality was not reduced significantly. There was a high discontinuation rate and increased risk of end-organ damage, particularly pulmonary and thyroid.

**CRD commentary**
The aims of the review were clearly stated in terms of study design, treatment and outcomes. A number of relevant sources were searched for published and unpublished studies. Only studies published in English were eligible and it was
possible that studies were missed. This may have resulted in language bias. The review methods aimed to reduce reviewer error and bias. Quality was assessed (although scoring systems are not considered to be the best methods for doing so). The methods of analyses appeared to be appropriate, any potential heterogeneity was investigated and clear details were presented for the included studies. Overall, although there were some limitations in the search for studies, the review appeared to be well conducted and the results are likely to be reliable.

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

**Practice:** The authors stated that people with cardiomyopathy at high risk of sudden cardiac death and who are not eligible for ICD implantation should be considered for amiodarone after assessing the risk/benefit ratio.

**Research:** The authors stated that the discrepancy in cancer-related deaths merited further study (four studies reported increased cancer deaths in amiodarone treatment groups).

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One author is listed as an inventor on a US provisional patent that covered methods for the prevention of sudden cardiac death.

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