Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials

Amiodarone Trials Meta-Analysis Investigators

Authors' objectives
To assess the benefits and risks of prophylactic amiodarone in patients with recent myocardial infarction (MI) or congestive heart failure (CHF).

Searching
The searches were described as a literature review, computerised literature search and discussion with colleagues. A collaborative group of principal investigators was established.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials were eligible. Of the included studies, nine were double-blind and placebo-controlled; the other four compared amiodarone with usual care (no anti-arrhythmic drugs).

Specific interventions included in the review
The inclusion criteria stated amiodarone compared with placebo or usual care. In the included studies, amiodarone was given initially as a loading dose (400 to 1,200 mg/day), then as a maintenance dose (200 to 400 mg/day). All the doses were oral with the exception of one study that used intravenous amiodarone in the initial period post-MI. The planned treatment time ranged from 6 months to 4.5 years.

Participants included in the review
People with recent MI or symptomatic compensated CHF were eligible for inclusion. In the included studies, 89% of the participants had had a previous MI. Some participants also had diabetes and non-ischaemic cardiomyopathy. The participants were male and female with mean ages ranging from 57 to 68 years.

Outcomes assessed in the review
The outcomes to be assessed were arrhythmic/sudden death, total mortality, non-arrhythmic death and adverse effects (hypothyroidism, hyperthyroidism, peripheral neuropathy, lung infiltrates, bradycardia and liver function).

How were decisions on the relevance of primary studies made?
The principal investigators of the identified studies were contacted.

Assessment of study quality
Original data for each individual patient were collected by the trial investigators using a previously defined protocol. No other details were given. The authors do not state how the data were assessed for validity.

Data extraction
The collaborative group established a protocol for collecting baseline, follow-up and outcome data. All data were extracted by each study group. The data were then consolidated into a master database by a coordinating centre.

Methods of synthesis
How were the studies combined?
The odds ratio (OR) and 95% confidence intervals (CIs) were calculated for each of the individual studies. The studies
were combined using the method described by Whitehead and Whitehead for survival data. Combined OR and 95% CI were calculated using the method described by Peto. Supplemental analyses, based on the random-effects models of DerSimonian and Laird, were also used where there was evidence of heterogeneity. All analyses were on an intention-to-treat basis unless otherwise stated.

**How were differences between studies investigated?**
Tests for heterogeneity were performed. Subgroup analyses were undertaken to investigate the influence of various baseline characteristics (e.g. diagnostic criteria, gender and age).

**Results of the review**
Thirteen studies (6,553 participants) were included: 8 studies (5,101 participants) of patients who had recently had a MI, and 5 studies (1,452 participants) of patients with CHF. Individual patient data were not available for two of these (small) studies; summary data from the original reports was used for these.

Total mortality was reduced by 13% (OR 0.87, 95% CI: 0.78, 0.99, p=0.03) when using the fixed-effect analysis, and by 15% (OR 0.85, 95% CI: 0.71, 1.02, p=0.081) when using the random-effects approach; both were in favour of amiodarone. Amiodarone reduced arrhythmic/sudden death by 29% when using the fixed-effect approach (OR 0.71, 95% CI: 0.59, 0.85, p=0.0003), or by 31% when using the random-effects approach (OR 0.69, 95% CI: 0.55, 0.87, p=0.0016). There was evidence of heterogeneity for this outcome (p=0.058), which the authors attributed to two small studies and one large study that used high-dose intravenous amiodarone in the immediate acute MI period. Following the exclusion of these studies there was no evidence of heterogeneity (p=0.093), but no summary OR was presented. There was no effect of amiodarone treatment on non-arrhythmic/non-sudden deaths (OR 1.02, 95% CI: 0.87, 1.19, p=0.84).

The subgroup analyses showed there was no difference in treatment effect between post-MI and CHF studies. The effectiveness of amiodarone was not influenced by left-ventricular ejection fraction, New York Heart Association class, or the presence or absence of asymptomatic ventricular arrhythmias on the Holter electrocardiogram.

The adverse effects associated with amiodarone use included hypothyroidism (net absolute difference 5.9%; p=0.00005 for OR), hyperthyroidism (net absolute difference 0.9% p=0.0043 for OR), Peripheral neuropathy (p=0.071), lung infiltrates (p=0.0003), bradycardia (p=0.0003) and liver dysfunction (p=0.0072) were all more common in the amiodarone groups. In the double-blind placebo trials, 41% of the amiodarone-assigned participants and 27% of controls permanently discontinued study medication (14% difference). This was primarily related to the adverse experiences associated with amiodarone.

**Authors' conclusions**
Prophylactic amiodarone reduces the rate of arrhythmic/sudden death in high-risk patients with recent MI or CHF, and does not affect the risk of other deaths. The net effect of amiodarone treatment in these patients results in an overall reduction of 13% in total mortality.

**CRD commentary**
The aims of this review were clearly stated and clear details of the included studies were given. Details of the search were not provided and it is possible that studies were missed. A collaborative group was set up to undertake an individual patient data review, which suggests a thorough approach, but some of the methods were not clearly defined in the paper. The authors noted significant heterogeneity in the results of studies investigating the effects of amiodarone on total mortality. However, the comparability of the results from fixed-effect and random-effects models provides some evidence to suggest that this did not affect the results to a large extent. The conclusions would appear to follow from the results.

**Implications of the review for practice and research**
Practice: Amiodarone would be a reasonable treatment in patients (with MI or CHF) who are at a particular high risk.
Research: The authors did not state any implications for further research.

Bibliographic details

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Other publications of related interest

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Subject indexing assigned by NLM

MeSH
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