Effectiveness of amiodarone for conversion of atrial fibrillation to sinus rhythm: a meta-analysis

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CRD summary
This review assessed the effectiveness of amiodarone in treating atrial fibrillation (AF). In this thorough and well-conducted review, the authors concluded that amiodarone is effective in treating AF in a wide range of patients. However, as information on adverse events was limited, further studies are required.

Authors’ objectives
To assess the effect of amiodarone in converting atrial fibrillation (AF) to sinus rhythm.

Searching
MEDLINE (January 1966 to February 2001), EMBASE (January 1980 to September 2000), the Cochrane Controlled Trials Register (Issue 3, 2000) and Best Evidence (January 1991 to September 2000) were searched using ‘atrial fibrillation’ and ‘amiodarone’ as MeSH terms or textwords. Articles indexed as ‘Randomised Controlled Trial’ (RCT) in the publication type or ‘drug therapy’ in the subject heading were also identified, as were articles with ‘random,’ ‘placebo’ or ‘trial’ in the title or abstract. Abstracts presented at major meetings of cardiology societies and published between 1995 and 2000 in Circulation, European Heart Journal, Journal of the American College of Cardiology, and Pacing and Clinical Electrophysiology, were handsearched. In addition, the reference lists from major cardiology and internal medicine textbooks, UpToDate version 2000 (volume 8, no.2), recent reviews of AF and all articles included in the review were searched. Experts in the field, the authors of the included articles, and a drug company were contacted in an attempt to identify unpublished studies. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised and quasi-randomised study designs were eligible for inclusion. However, the numbers and types of quasi-randomised trials were not described.

Specific interventions included in the review
Studies of amiodarone compared with placebo, digoxin, calcium-channel blockers, or no treatment were eligible for inclusion. Amiodarone was administered orally or intravenously.

Participants included in the review
Studies of patients with AF of any aetiology and duration were eligible for inclusion. Studies were excluded if more than 30% of participants had non-AF supraventricular arrhythmias, or were concerned with the primary prevention of AF. The mean age of the patients ranged from 58 to 71 years and the proportion of males from 43 to 86%. Most of the studies included patients with and without underlying cardiovascular diseases.

Outcomes assessed in the review
The primary outcome was the conversion of AF to sinus rhythm within a 4-week period. The authors also assessed the effects on mortality and adverse events within a 4-week period. Adverse effects included severe ventricular arrhythmia, other ventricular arrhythmia, supraventricular arrhythmia, bradyarrhythmias, symptomatic hypotension or hypotension requiring treatment, or systolic blood-pressure less than 90 mmHg, major cardiovascular events, or other adverse events requiring the withdrawal of or a reduction in drug treatment. The outcome closest to 4 weeks after the intervention was included in analyses. For adverse events the total number of events was considered. Studies were excluded if insufficient primary outcome data were available after contacting the authors.

How were decisions on the relevance of primary studies made?
Two of the three reviewers read each title and/or abstract identified in the search. In the case of disagreements, two
authors made a further assessment on the basis of the full publication or abstract, and any disagreements were resolved by consensus. When necessary, the authors of the trials were contacted for further information. The study selection process was depicted in a diagram and reasons for exclusion were listed. Kappa scores for agreement were presented.

**Assessment of study quality**
Validity was judged on the basis of the following: randomisation procedure; concealment of treatment allocation, blinding of the patient, caregiver and outcome assessor; and completeness of follow-up. Two authors independently judged validity and, if necessary, after obtaining information from the trial authors, resolved any disagreements by consensus. The extent of agreement was recorded.

**Data extraction**
The data were extracted in duplicate, independently, by two of the three authors. The relative risk (RR) for conversion to sinus rhythm and 95% confidence intervals (CIs) were calculated for individual studies using the intention-to-treat principle. Where a study reported data at more than one time point, the measurement closest to 4 weeks was used. For a study with more than one amiodarone or control arm, the data from the arms were pooled.

**Methods of synthesis**
How were the studies combined?
The RRs in each study were combined using the random-effects model of DerSimonian and Laird. Funnel plots were used to investigate publication bias. Supplementary analyses in which absolute risk differences were pooled using random-effects models, were also carried out. The results were analysed on an intention-to-treat basis.

How were differences between studies investigated?
Among studies with results significant at a P-value of less than 0.05, heterogeneity was assessed by a chi-squared test. Possible explanations for heterogeneity were investigated according to a priori hypotheses: baseline prognostic characteristics (duration of AF, left atrial size, underlying cardiovascular disease); control treatment (placebo or no treatment, digoxin or calcium-channel blocker); amiodarone regimen (single dose versus continuous oral or intravenous); and follow-up time (less than 12 hours or 12 hours or more).

**Results of the review**
Twenty-one studies with 2,000 patients were included. The outcomes were reported for 1,930 patients (1,002 and 928 patients randomised to amiodarone and control, respectively).

There was significant heterogeneity among the study results and the authors pooled studies into two groups according to the mean duration of AF. The short AF duration group (48 hours or less) included 16 studies of 1,344 patients, while the long AF duration group (48 hours to 4 weeks) included 5 studies of 586 patients. For conversion to sinus rhythm, the pooled estimates of RR in patients with short and long AF duration were 1.40 (95% CI: 1.25, 1.57) and 4.33 (95% CI: 2.76, 6.77), respectively. Significant heterogeneity was apparent in studies of short AF duration (P=0.009). The risk differences in the short and long AF duration groups were 0.26 (95% CI: 0.18, 0.34) and 0.27 (95% CI: 0.08, 0.47), respectively, and the numbers-needed-to-treat were 4 (95% CI: 3, 6) and 4 (95% CI: 3, 14).

Mortality as an outcome was reported in 12 studies of 1,512 patients. As only 5 of the patients randomised to amiodarone (n=816) and 5 of the control patients (n=696) died, the authors did not conduct an analysis. No evidence was found for increased adverse events in patients randomised to amiodarone treatment compared with controls, but appropriate analyses were not possible as adverse events were uncommon.

The funnel plot showed no evidence of publication bias for the primary outcome.

**Authors' conclusions**
Amiodarone was effective in converting AF to sinus rhythm in a wide range of patients.
CRD commentary
This review was clearly written and had well-defined aims. The review process, including the literature search, study selection and data extraction, was described in detail and the course of the review shown in a flow diagram. The authors attempted to identify unpublished information in addition to published trials, and contacted authors at both the inclusion and data extraction stages of the review. A funnel plot was shown for the primary outcome, in order to assess publication bias. A detailed quality assessment was carried out and the results were considered in terms of possible sources of heterogeneity. Appropriate details of the studies were tabulated. The methods used to pool the results were appropriate and heterogeneity was formally investigated.

The authors’ conclusions are supported by the results presented.

Implications of the review for practice and research
Practice: The authors stated that amiodarone was recommended as the first-line treatment of AF for stable patients without thyroid disease or conduction abnormalities.

Research: The authors stated that a more detailed exploration of adverse events in trials of amiodarone in the conversion of AF to sinus rhythm are needed.

Bibliographic details

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Other publications of related interest
This additional published commentary may also be of interest. Newman D. Review: Amiodarone is effective for converting atrial fibrillation to sinus rhythm. ACP J Club 2004;140:6.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.