Pharmacologic conversion of atrial fibrillation: a systematic review of available evidence
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Authors' objectives
To evaluate the efficacy of currently available anti-arrhythmic agents for the conversion of atrial fibrillation (AF) to normal sinus rhythm (NSR).

Searching
MEDLINE (from 1996 to May 2001), EMBASE (from 1966 to May 2001), and Current Contents (from 1966 to September/October 2001) were searched for articles published in the English language. Full details of the keywords used were provided. The reference lists of all identified studies, recent review articles and personal files were examined. Additional trials were identified by contacting experts and conducting manual searches. Unpublished studies and duplicate studies were excluded.

Study selection
Study designs of evaluations included in the review
The inclusion criteria were not defined a priori in terms of the study design. The included studies were: randomised placebo-controlled trials; randomised comparative trials; prospective, non-randomised comparative trials; prospective cohort trials; reviews of retrospective data; and case series.

Specific interventions included in the review
Treatments with anti-arrhythmic agents specifically aimed at converting AF to NSR were eligible. Drugs that were currently unavailable or were without a new drug application submission in the United States were excluded. Studies exclusively describing drug therapies for conversion of AF associated with cardiac surgery were also excluded. The following anti-arrhythmic agents were included: oral quinidine; oral disopyramide; intravenous procainamide; oral flecaïnine; oral propafenone; oral sotalol; intravenous and oral amiodarone; intravenous ibutilide; and oral dofetilide.

Participants included in the review
Patients with AF were eligible. Studies that exclusively involved patients with AF after cardiac surgery were excluded. Patients with the following types of AF were included: recent onset (less than 7 days); recent-onset AF of longer duration; chronic AF; paroxysmal AF; and heterogeneous AF.

Outcomes assessed in the review
Studies that assessed conversion rates from AF to NSR were eligible. The end points ranged from 1 hour to 30 days in placebo-controlled, randomised controlled trials. Adverse events were also 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 reviewers performed the selection.

Assessment of study quality
Study quality was assessed on the basis of the following criteria: baseline comparability of the treatment groups; the method of randomisation (randomised versus non-randomised); the adequacy of blinding; clinical outcomes; statistical power; the completeness of follow-up; and the method of analysis. The studies were classified according to their methodological rigour using a levels-of-evidence scheme (see Other Publications of Related Interest nos. 1-3). This assigned five levels of evidence: level 1 for prospective, randomised placebo-controlled trials; level II for prospective, randomised comparative trials; level III for prospective, non-randomised comparative trials; level IV for prospective cohort trials; and level V for retrospective data or case series. Any discrepancies in the quality criteria were resolved by group consensus. The authors do not state how many of the reviewers performed the quality assessment.
Data extraction
Any discrepancies in the data extraction were resolved by group consensus. The authors do not state how many of the reviewers performed the data extraction.

The following data were extracted (where available): author and year of publication; study design; the characteristics of the participants; therapeutic intervention and cointerventions; the type of control group; the duration of AF; the number of patients; the time at which the end point was assessed; the success rate and median or mean time to conversion; and the conversion time. In trials that included both AF and atrial flutter, data for the subgroup of patients with AF were extracted. Attempts were made to obtain additional information from the authors. The absolute risk reduction, number-needed-to-treat, and 95% confidence intervals (CIs) were calculated for conversion rates in level I studies.

Methods of synthesis
How were the studies combined?
The studies were grouped by anti-arrhythmic agent, then separated according to the level of evidence (level I and II versus lower level studies) and combined in a narrative review. Subsequently, evidence from 24 level I studies (3,720 patients with AF) was used to make recommendations for treatment for the following groups of patients: recent-onset AF (less than 7 days); recent-onset AF of longer duration (less than 90 days); chronic AF; and patients with left ventricular dysfunction.

How were differences between studies investigated?
Differences between the studies were discussed in the text of the review.

Results of the review
A total of 88 studies were included, including 34 level I and 13 level II studies.

The methodological flaws identified were as follows: small sample size and a lack of statistical power; populations that were varied and ill-defined; CIs were not reported for the results and there were no data from which they could be calculated; most of the trials had short-term follow-up; and the reporting of adverse reactions was often incomplete.

The following results were from selected, well-designed level I studies only, i.e. randomised placebo-controlled trials (RCTs).

Patients with recent-onset AF (less than 7 days).
The following drugs were effective in converting recent-onset AF to NSR within 24 hours: quinidine (1 RCT), intravenous procainamide (1 RCT), flecainide (3 RCTs), propafenone (9 RCTs), high-dose intravenous amiodarone (1 RCT), a combination of intravenous plus oral amiodarone (1 RCT), and high-dose oral amiodarone (1 RCT).

Patients with recent-onset AF of longer duration (less than 90 days). Intravenous ibutilide (3 RCTs) was effective for converting recent-onset AF of less than 90 days duration. Confidence intervals were reported for the absolute risk reduction at 90 minutes (95% CI: 27, 29) and the number-needed-to-treat (95% CI: 3, 4).

Patients with AF of longer duration.
The following drugs were effective in converting chronic AF to NSR: oral propafenone (1 RCT), intravenous and oral amiodarone (2 RCTs), and dofetilide (2 RCTs). Compared with placebo, there was no difference in the conversion rates for either propafenone or amiodarone until after 30 days of therapy.

Patients with left ventricular dysfunction.
No studies were identified that exclusively evaluated anti-arrhythmic agents in this group of patients. Dofetilide (subgroup of 2 RCTs): the absolute risk reduction at 72 hours was 20% and the number-needed-to-treat was 5.

Adverse reactions.
In level I trials, there were no differences between the treatment and placebo groups in the rates of minor or major adverse reactions, or withdrawals due to adverse effects. Adverse events associated with individual drug therapies were discussed in the text.

Authors’ conclusions
For conversion of recent-onset AF of less than 7 days, the preferred intravenous and oral agents were considered to be procainamide and propafenone, respectively. For conversion of recent-onset AF of longer duration (less than 90 days), intravenous ibutilide may be considered the preferred agent. For patients with chronic AF and left ventricular dysfunction, direct cardioversion was the preferred conversion method.

CRD commentary
The aims were stated and the inclusion criteria were defined in terms of the intervention, participants and outcome, but inclusion criteria for study design were not defined a priori. Several relevant sources of literature were searched and full details of the keywords used were given, but the methods used to select the studies were not described. The authors acknowledged that restricting the included studies to those published in the English language may have resulted in the omission of other relevant studies, and that the lack of an attempt to locate unpublished material raises the possibility of publication bias.

Quality was assessed using defined criteria and the studies were classified according to their design. The methods used to assess quality were described but the results of the assessment were not reported. The studies were initially grouped by pharmaceutical agent and combined in a narrative review. Subsequently, evidence from placebo-controlled RCTs was used to make recommendations. Most recommendations were based on results from a single RCT; the recommendations were not based on good-quality studies that directly compared pharmaceutical agents. Hence, the authors’ conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors state that for conversion of recent-onset AF of less than 7 days, procainamide may be considered a preferred intravenous agent and propafenone a preferred oral agent. For conversion of recent-onset AF of longer duration (less than 90 days), intravenous ibutilide may be considered the preferred agent. For patients with chronic AF and left ventricular dysfunction, direct cardioversion was the preferred conversion method.

Research: The authors state that larger, well-designed RCTs with a clinically important end point are required in specific populations of AF patients.

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Other publications of related interest
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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.