Management of new onset atrial fibrillation

Authors' objectives
To synthesise the evidence that exists to guide clinicians in the management of patients with new onset atrial fibrillation (AF). The key questions to be addressed were identified as follows.

Which patients should receive cardioversion and which should receive conservative treatment with rate control and thromboembolism prophylaxis?

What is the efficacy of electrical cardioversion alone versus anti-arrhythmic treatment alone versus both together in this patient group?

What are the risks and benefits of each anti-arrhythmic agent used for conversion of AF and/or the maintenance of sinus rhythm after successful cardioversion?

What types of therapy for AF can be performed safely in an out-patient rather than an in-patient setting?

What is the diagnostic value of tests, such as transoesophageal and transthoracic echocardiography, that can be used in the evaluation of patients with new onset AF? There were also supplementary questions to be addressed.

How does anticoagulation compare with aspirin in preventing thromboembolism in patients with AF?

How do each of the pharmacological agents used in rate control compare in efficacy?

Searching
The following sources were searched: the Cochrane Controlled Trials Register from 1948 to 1998, which was accessed via the Cochrane Library (Issue 1 and 2, 1998); MEDLINE from 1966 to 1998; the 'related articles' feature of PubMed for each article retrieved from the previous two searches; and articles submitted to the Cardiovascular Randomised Controlled Trial Register at the Baltimore Cochrane Centre. The following search strategy was used: 'atrial fib' (MeSH) or 'atrial fibrillation' (textword) or 'atrial flutter' (textword) combined with the Cochrane optimal search strategy for retrieval of controlled trials. Additional search strategies for key questions 4 and 5, which were not limited to RCTs, were also conducted. The search strategies were provided in the appendices of the review.

The reference lists of relevant meta-analyses, reviews and major trials, and the tables of contents of the journals most frequently cited in the searches were also examined. In addition, investigators in the field and search coordinators of relevant Cochrane Collaborative Review Groups were asked to identify trials that had been completed but not published. Final programmes of the American College of Cardiology and American Heart Association were reviewed to search for abstracts suggesting unpublished data.

English abstracts of non-English language articles were reviewed. Full papers were not obtained and data were not extracted from these abstracts. However, comments on these studies were included in the narrative summary of the studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs).

For key questions 4 and 5 (i.e. out-patient initiation of treatment and use of echocardiography), the search for RCTs did not yield many studies so further searches encompassing all study designs were performed.
Specific interventions included in the review

The interventions for pharmacological conversion of AF were: quinidine alone or with digoxin, verapamil, direct current conversion (DCC), or practolol; procainamide; disopyramide; flecainide alone or with digoxin; propafenone; amiodarone; sotalol alone or with digoxin; ibutilide; dofetilide; verapamil alone or with quinidine; pirmenol; pilsicainide; timolol; magnesium; diltiazem; and digoxin. The comparison groups were: placebo alone or with digoxin; propafenone; amiodarone; sotalol; verapamil alone or with DCC; DCC; flecainide; diltiazem; digoxin alone or with quinidine; quinidine; and cibenzoline.

The interventions for pharmacological maintenance of sinus rhythm were: quinidine alone or with digoxin, verapamil, or DCC; disopyramide; flecainide; propafenone; sotalol plus digoxin; bisoidomide; and amiodarone. The comparison groups were: flecainide; placebo plus digoxin; propafenone; sotalol; verapamil; DCC; quinidine; N-acetylprocainamide; and cibenzoline.

The interventions for rate control were: diltiazem alone or with digoxin; verapamil alone or with digoxin; xamoterol; atenolol; timolol; nadolol alone or with digoxin; celiprolol; pindolol alone or with digoxin; labetalol alone or with digoxin; propranolol; clonidine; propafenone; sotalol; betaxolol alone or with digoxin; magnesium sulphate alone or with digoxin; and metoprolol. The comparison groups were: placebo, digoxin, disopyramide; flecainide; verapamil; quinidine; propranolol alone or with digoxin; and amiodarone.

The interventions for antithrombotic therapy were warfarin, aspirin and low molecular weight heparin (LMWH). The comparison groups were aspirin, placebo, aspirin plus low-dose warfarin, and indobufen.

The treatment regimes for these comparisons were listed in tabular format.

Participants included in the review

AF. The participants included in the review were all ambulatory adults who presented with new onset, non post-operative AF. This included those with persistent and paroxysmal AF, with or without atrial flutter. The patients were included regardless of whether the duration of the arrhythmia was known or unknown.

Outcomes assessed in the review

Not all definitions of the outcomes assessed were clearly stated. The outcomes for each intervention studied were as follows.

Pharmacological conversion of AF: successful conversion. Adverse events were looked for but were poorly reported.

Maintenance of sinus rhythm: no recurrence of AF.

Rate control: mean heart rate at rest, while on medication; the proportion who reached their goal in terms of heart rate reduction; and the maximum heart rate with exercise.

Anticoagulation or antiplatelet therapy: stroke or haemorrhage.

Use of echocardiography: no useful outcome was identified (Reviewer's statement).

Out-patient initiation of treatment: frequency of ventricular arrhythmia was used in some trials. No useful outcome was identified (Reviewer's statement).

How were decisions on the relevance of primary studies made?

Two reviewers reviewed the abstracts according to the inclusion and exclusion criteria, and any discrepancies were resolved by consensus.

Assessment of study quality

A quality assessment form was devised, based on ones used previously by the authors, other citations, consensus discussions, Cochrane Collaboration advice, and the key questions proposed by Detsky et al. (see Other Publications Of Related Interest). The final quality assessment form contained 22 questions covering the following topics:
representativeness of the study population, i.e. how completely the authors described the study participants; bias and confounding, which included a requirement for a description of the randomisation and degree of masking; description of therapy, which included a description of the protocol and other therapies received; outcomes and follow-up, including an explicit description of the outcomes and patients withdrawing; and statistical quality and interpretation.

Each question was assigned a value of between 0 and 2. The score assigned to each paper was the percentage of the total points available in each category. The overall quality score was the average of the five categorical scores. Two independent reviewers performed the quality assessment and any disagreements were resolved by consensus.

**Data extraction**

The data were extracted by one reviewer and checked by a second. The following data were abstracted: participant inclusion and exclusion criteria; baseline participant characteristics; baseline left atrial size; the duration of left atrial fibrillation or flutter; the percentage of participants with atrial flutter; co-morbid illnesses; therapeutic protocols; goal time of follow-up; main outcomes; and secondary outcomes, including adverse events necessitating either cessation of the drug or a reduction in the dose. The data for each key question were presented in evidence tables, which were populated directly from the database of article abstraction forms. Accuracy of the tables was confirmed by comparison with the original articles.

**Methods of synthesis**

How were the studies combined?

The odds ratios (ORs) for the following outcomes were combined using fixed-effect models: conversion to sinus rhythm; maintenance of sinus rhythm; stroke; peripheral embolism; major bleeding; minor bleeding; and mortality. Random-effects models were used in two cases where the data showed quantitative heterogeneity. The studies were weighted on the basis of study size and the precision of the estimate in each study. The pooled ORs were also converted into number-needed-to-treat data.

How were differences between studies investigated?

The evidence tables were examined for heterogeneity (qualitative assessment). Within-group heterogeneity was assessed using a chi-squared test. Where significant heterogeneity was found, random-effects models were used for pooled estimates. Subgroup analyses were undertaken to evaluate the impact of baseline characteristics of the study participants on aggregate study outcomes.

**Results of the review**

There were 47 studies (3,476 patients) of pharmacological conversion, 30 studies (3,470 patients) of maintenance of sinus rhythm, 63 studies (1,880 patients) of heart rate control, and 11 studies (8,690 patients) of antithrombotic therapy.

No RCTs were identified for out-versus in-patient strategies. However, 2 observational studies with 717 patients or drug trials were identified.

For echocardiography, there were 6 studies evaluating acute cardioversion and 2 studies evaluating maintenance of sinus rhythm; the numbers of patients were not reported. 'Many' trials reported on the use of echocardiography to predict embolic events. Results from a pooled analysis of 3 trials with 167 patients were presented. No trials regarding the use of transoesophageal echocardiography to guide timing of acute cardioversion were identified.

All results were presented as the combined OR with the 95% confidence interval (CI).

Pharmacological conversion.

Compared with control, the OR was 2.9 (95% CI: 1.2, 7.0) for quinidine, 7.0 (95% CI: 0.3, 153.0) for disopyramide,
24.7 (95% CI: 9.0, 68.3) for flecainide, 4.6 (95% CI: 2.6, 8.2) for propafenone, 5.7 (95% CI: 1.0, 33.4) for amiodarone, 0.4 (95% CI: 0.0, 3.0) for sotalol, and 29.1 (95% CI: 9.8, 86.1) for ibutilide or dofetilide. For quinidine, the OR was 0.4 (95% CI: 0.1, 2.0) versus propafenone, 0.2 (95% CI: 0.1, 0.9) versus amiodarone, and 5.8 (95% CI: 2.4, 14.2) versus sotalol.

For flecainide, the OR was 7.4 (95% CI: 1.9, 28.3) versus procainamide, 5.1 (95% CI: 2.3, 11.0) versus propafenone, and 2.5 (95% CI: 0.2, 29.6) versus amiodarone. For propafenone versus amiodarone, the OR was 13.1 (95% CI: 2.1, 79.6).

Other comparisons of the efficacy of miscellaneous drugs and combination drugs (with and without DCC) on pharmacological conversion were also detailed in the review.

Maintenance of sinus rhythm. Compared with control, the OR was 4.1 (95% CI: 2.5, 6.7) for quinidine, 3.4 (95% CI: 1.6, 7.1) for disopyramide, 3.1 (95% CI: 1.5, 6.2) for flecainide, 3.7 (95% CI: 2.4, 5.7) for propafenone, and 7.1 (95% CI: 3.8, 13.4) for sotalol.

For quinidine, the OR was 0.7 (95% CI: 0.4, 1.2) versus flecainide, 0.3 (95% CI: 0.1, 0.7) versus propafenone, 0.9 (95% CI: 0.5, 1.5) versus sotalol, and 0.9 (95% CI: 0.1, 16.5) versus amiodarone.

For disopyramide, the OR was 1.8 (95% CI: 0.6, 5.1) versus propafenone, and 0.3 (95% CI: 0.1, 1.0) versus amiodarone.

For flecainide versus propafenone, the OR was 0.9 (95% CI: 0.4, 2.2).

For propafenone versus sotalol, the OR was 0.7 (95% CI: 0.4, 1.1).

For long- versus short-acting quinidine, the OR was 3.5 (95% CI: 0.9, 13.0).

For flecainide versus cibenzoline, the OR was 1.4 (95% CI: 0.5, 4.0).

The results from the trials of rate control were too disparate for meta-analyses. Diltiazem and verapamil were more efficacious than placebo or digoxin in reducing the heart rate at rest and during exercise in patients with AF. Beta-blockers were more efficacious than placebo or digoxin in reducing the heart rate during exercise in patients with AF. Exercise tolerance was decreased in patients on beta-blockers in a number of studies. The effect of beta-blockers on resting heart rate was inconsistent. The evidence was inconclusive regarding the efficacy of digoxin, particularly during exercise.

Warfarin versus placebo for various outcomes.

The OR was 0.30 (95% CI: 0.19, 0.48) for stroke, 0.50 (95% CI: 0.19, 1.35) for peripheral embolism, 1.90 (95% CI: 0.89, 4.04) for major bleeding, 2.01 (95% CI: 1.51, 2.69) for minor bleeding, and 0.62 (95% CI: 0.38, 1.02) for mortality.

Aspirin versus placebo for various outcomes.

The OR was 0.65 (95% CI: 0.43, 0.99) for stroke, 1.02 (95% CI: 0.33, 3.17) for peripheral embolism, 0.81 (95% CI: 0.37, 1.77) for major bleeding, 3.01 (95% CI: 0.12, 7.4) for minor bleeding, and 0.79 (95% CI: 0.51, 1.22) for mortality.

Warfarin versus aspirin for various outcomes.

The OR was 0.64 (95% CI: 0.43, 0.96) for stroke, 1.27 (95% CI: 0.31, 5.16) for peripheral embolism, 1.60 (95% CI: 0.77, 3.35) for major bleeding, 1.80 (95% CI: 1.05, 3.11) for minor bleeding, and 0.96 (95% CI: 0.58, 1.56) for mortality.
Warfarin versus low-dose warfarin and aspirin for various outcomes.

The OR was 0.35 (95% CI: 0.21, 0.59) for stroke, 1.00 (95% CI: 0.17, 5.81) for peripheral embolism, 1.14 (95% CI: 0.55, 2.36) for major bleeding, 1.68 (95% CI: 0.98, 2.86) for minor bleeding, and 1.02 (95% CI: 0.68, 1.52) for mortality.

Warfarin versus indobufen for various outcomes.

The OR was 0.56 (95% CI: 0.25, 1.22) for stroke, 0.63 (95% CI: 0.21, 1.95) for peripheral embolism, 5.13 (95% CI: 0.60, 44) for major bleeding, 6.68 (95% CI: 1.96, 22) for minor bleeding, and 0.93 (95% CI: 0.56, 1.52) for mortality.

LMWH vs placebo for various outcomes.

The OR was 0.34 (95% CI: 0.06, 1.83) for stroke, 0.56 (95% CI: 0.05, 6.44) for peripheral embolism, and 3.93 (95% CI: 0.74, 20) for mortality.

The echocardiography results suggested an inverse association between left-atrial diameter and successful cardioversion. No conclusions were reached with regards to comparisons of initiating therapy in an in-patient versus an out-patient setting.

Cost information
The following results were obtained from decision analyses.

One attempt of electrical cardioversion with pharmacological maintenance therapy was cost-effective when compared with conservative antithrombotic therapy alone for all patients aged 55 years or older, regardless of the risk factors.

Transthoracic echocardiography is projected to be a cost-effective test for guiding decisions about the choice of antithrombotic treatment in patients with and without risk factors for thromboembolism.

If anti-arrhythmic therapy can be started safely as an out-patient, the cost-effectiveness of an attempt of electrical cardioversion with pharmacological maintenance therapy is improved considerably.

For patients at low risk of stroke, aspirin is the most cost-effective therapy. For those at high risk of stroke, warfarin is projected to be the most cost-effective strategy.

Authors' conclusions
For pharmacological conversion of AF, compared with controls, the evidence for efficacy was strongest for flecainide, ibutilide or dofetilide, and propafenone. There was moderate evidence of efficacy for quinidine, and suggestive evidence of efficacy for disopyramide and amiodarone. There was suggestive evidence of negative efficacy for sotalol and minimal evidence for other drugs.

For pharmacological maintenance of sinus rhythm, compared with controls, the evidence for efficacy was strongest for quinidine, disopyramide, flecainide, propafenone and sotalol. There was minimal evidence for drug classes of miscellaneous drug combinations. Compared with disopyramide, the authors found potentially strong evidence for efficacy of amiodarone.

Rate control: diltiazem and verapamil were more efficacious than placebo or digoxin in reducing the heart rate at rest and during exercise in patients with AF. Beta-blockers were more efficacious than placebo or digoxin in reducing the heart rate during exercise in patients with AF. Exercise tolerance was decreased with beta-blockers in a number of studies. The effect of beta-blockers on resting heart rate was inconsistent. The evidence was inconclusive regarding the efficacy of digoxin, particularly during exercise.

There was strong evidence of the efficacy of warfarin in preventing stroke when compared with placebo. The evidence suggested a higher bleeding rate for patients on warfarin. There was suggestive evidence of the efficacy of aspirin in
preventing stroke when compared with placebo. The evidence surrounding the bleeding rate was inconclusive. Comparisons of aspirin and warfarin did not permit strong conclusions. The evidence did not support the use of a combination of low-dose warfarin and aspirin or the use of LMWH or induprofen for stroke prevention, but the data are limited.

The results of echocardiography studies suggested an inverse association between left-atrial diameter and successful cardioversion.

No conclusions were reached with regards to comparisons of initiating therapy in an in-patient versus an out-patient setting.

**CRD commentary**
This was a well-conducted, thorough review. The search appears to have been thorough, and it is unlikely that any major trials were missed because of the search strategy. The authors addressed the questions of publication and language bias, and their results suggest that neither will have biased the results of the review. Application of the inclusion and exclusion criteria, the quality assessment, and the data extraction were performed by two reviewers. All relevant data were presented in the evidence tables. Importantly, the definitions of the outcomes assessed were not clearly stated, e.g. it is unclear whether conversion to sinus rhythm must occur within a given time period to be included as a successful outcome.

The results were presented clearly for each study as well as the combined analyses.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors state the following implications.

**Pharmacological conversion.**

Further trials are needed to compare flecainide and ibutilide or dofetilide for acute conversion of AF; and to evaluate amiodarone for acute conversion of AF and maintenance of sinus rhythm. Future trials ought to be stratified by risk factors for adverse events, and ought to assess quality-of-life outcomes. Trials with longer follow-up for maintenance of sinus rhythm are also required.

**Rate control.**

Future trials ought to assess quality-of-life outcomes, and outcomes such as functional status and exercise tolerance. Dual roles of medications (e.g. oral propafenone and amiodarone) in pharmacological conversion and rate control need to be evaluated. Confirmatory studies of the rate-controlling effect of sotalol are required.

**Anti-coagulants and anti-platelet drugs.**

Additional studies of warfarin and aspirin in moderate- and low-risk populations are needed, as are comparisons of LMWH with aspirin, warfarin and placebo. A study of indobufen for primary prevention of stroke may be warranted. Studies of other antithrombotic drugs (e.g. ticlopidine and clopidogrel) are required for those patient groups unable to take warfarin.

**Other.**

The safety and cost of initiating anti-arrhythmic therapy in the out-patient setting need to be investigated. RCTs to study the effects of using transthoracic and transoesophageal echocardiography on outcomes are required, in order to help guide decisions about the choice of antithrombotic treatments.
Bibliographic details

Original Paper URL
http://www.ahrq.gov/clinic/epcsums/atrialsum.htm

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.