Meta-analysis of randomised controlled trials of the effectiveness of antiarrhythmic agents at promoting sinus rhythm in patients with atrial fibrillation

G Nichol, F McAlister, B Pham, A Laupacis, B Shea, M Green, A Tang, G Wells

Objective: To conduct a meta-analysis of randomised controlled trials to estimate the effectiveness of antiarrhythmic agents at promoting sinus rhythm in patients with atrial fibrillation.

Design: Articles were identified by using a comprehensive search of English language papers indexed in Medline from 1966 to August 2001. For the outcomes of sinus rhythm and death, a random effects model was used to model repeated assessments within a study at different time points.

Setting: Emergency departments and ambulatory clinics.

Patients: Patients with atrial fibrillation.

Interventions: Antiarrhythmic agents grouped according to their Vaughan-Williams class.

Main outcome measures: Sinus rhythm and mortality.

Results: 91 articles met a priori criteria for inclusion in the analysis. Median duration of follow up was one day (range 0.04–1096, mean [SD] 46 [163] days). The median proportion of patients in sinus rhythm at follow up was 55% (range 0–100%) and 32% (range 0–90%) receiving active treatment and placebo, respectively. Median survival was 99% (range 55–100%) and 99% (range 55–100%). Compared with placebo, the following drug classes were associated with increased sinus rhythm at follow up: IA (treatment difference 21.5%, 95% confidence interval [CI] 16.3% to 26.8%); IC (treatment difference 33.1%, 95% CI 23.3% to 42.9%); and III (treatment difference 17.4%, 95% CI 11.5% to 23.3%). Class IC drugs were associated with increased sinus rhythm at follow up compared with class IV drugs (treatment difference 43.2%, 95% CI 11.5% to 75.0%). There was no significant difference in mortality between any drug classes.

Conclusions: Class IA, IC, and III drugs are associated with increased sinus rhythm at follow up compared with placebo. It is unclear whether any antiarrhythmic drug class is associated with increased or decreased mortality.

Atrial fibrillation is the most common cardiac arrhythmia and can be associated with disabling complications. At least 5% of admissions for cardiovascular disease are for management of atrial fibrillation. Patients in atrial fibrillation can receive treatment to decrease embolic complications, to promote sinus rhythm, or to control ventricular rate. Each of these treatments is associated with particular risks and benefits. Although the effectiveness of anticoagulant treatment in atrial fibrillation is well established, use of electrical cardioversion or antiarrhythmic drugs may offer additional benefits. Compared with patients with atrial fibrillation, patients in whom sinus rhythm is restored have fewer strokes, greater cardiac output, and reversal of cardiomyopathy. However, attempts to maintain sinus rhythm may be associated with increased mortality. Furthermore, as many as 75% of patients relapse into chronic atrial fibrillation within 12 months of restoration of sinus rhythm. Any reduction in the mortality or morbidity caused by stroke that is attained by use of antiarrhythmic drugs may be offset by adverse drug effects or relapse to atrial fibrillation.

Antiarrhythmic treatment to restore and maintain sinus rhythm after atrial fibrillation has been evaluated in many small trials. These trials evaluated several drugs, each of which has unique mechanisms of action and side effects. A large trial underway is evaluating the effectiveness of antiarrhythmic agents in patients with atrial fibrillation. In the AFFIRM study (atrial fibrillation follow-up investigation of rhythm management), the choice of antiarrhythmic drug was at the discretion of the physician. Therefore, the results of this study are unlikely to determine whether a specific antiarrhythmic drug has long term effectiveness in atrial fibrillation. Despite ongoing and previous trials, there is major interphysician variability in prescribing behaviours related to antiarrhythmic treatment in patients with atrial fibrillation.

Meta-analysis is a method of pooling the results of individual trials statistically to provide an overall estimate of the effectiveness of a treatment. The combination of several studies can yield additional power to detect significant differences between treatments. Therefore, the purpose of this meta-analysis was to estimate the effectiveness of various classes of antiarrhythmic drugs in patients with atrial fibrillation. Using a protocol that was developed a priori, we conducted a meta-analysis based on conventional techniques. The protocol consisted of selection criteria for the primary studies, definitions of the primary end points, and an analysis plan.

METHODS
Identification of trials

Our aim was to identify all randomised controlled trials for which results were available by August 2001. A randomised controlled trial was defined as a research study in which patients were assigned prospectively to a treatment group by random allocation. Studies were identified by using a comprehensive search of English language articles indexed in Medline for the keywords “atrial fibrillation” and “antiarrhythmic agents”. Potentially relevant randomised trials were identified by combining these keywords with the
Cochrane Collaboration’s search strategy. Only references published in the English language were considered. The bibliographies of published studies were reviewed to identify additional references. The authors of the primary studies were not contacted to identify additional studies. All published primary studies, but not unpublished studies or abstracts, were considered for inclusion in the analysis.

Classification of antiarrhythmic agents

All antiarrhythmic agents were grouped according to their mechanism of action by using the Vaughan-Williams classification system. Accordingly, drugs that were studied were classified as class I, which block sodium channels; class II, which block β receptors (for example, practolol); class III, which prolong repolarisation (for example, amiodarone, dofetilide, ibutilide, sotalol, and lidoflazine); class IV, which block calcium channels (for example, clonidine, diltiazem, magnesium, and verapamil); and other agents (for example, digoxin). Class I agents were subclassified as IA, which depress action potential upstroke, slow conduction, and prolong repolarisation (for example, cibenzoline, disopyramide, procainamide, and quindine); and class IC, which depress upstroke depolarisation, slow conduction, and have a slight effect on repolarisation (for example, flecainide, pilsicainide, and propafenone).

Inclusion and exclusion criteria

A priori exclusion criteria were studies that did not use a randomised study design; enrolled patients with induced atrial fibrillation; evaluated treatments other than antiarrhythmic agents; evaluated use of antiarrhythmic agents for prophylaxis of atrial fibrillation alone; followed up patients for < 60 minutes after drug administration; or lacked data on the proportion of patients in sinus rhythm at study follow up.

Study quality

The quality of each primary study was evaluated by using the Quality Assessment of Observational Studies in Epidemiology (QASE) tool. This is a three item scale that measures the methodological quality of clinical studies. Individual items are randomisation, blinding, and withdrawal and dropout. Allocation concealment was also included (with two additional bonus points). Therefore, the maximum number of points per study was seven. Numbers were abstracted twice by two independent reviewers, and checked for accuracy after data entry.

Outcomes and data abstraction

The following variables were extracted from each study, if available: type and dose of intervention and control drugs; type and dose of concomitant drugs; number, age, and sex of patients; number of patients who dropped out; number of patients who withdrew; number of patients in sinus rhythm at each follow up; and number of patients deceased. For the purpose of this analysis, patients were considered to have dropped out of the study if they were lost to follow up. Patients were considered to have withdrawn if they stopped taking the study drug.

All studies were independently reviewed for eligibility, data abstraction, and study quality (by MG, FM, GN, BS, and AT). Differences were resolved by discussion until consensus was achieved. Data were abstracted twice and checked for accuracy after data entry.

Primary analyses

Data were analysed by using the SAS mixed procedure. Primary analyses compared the effect of each class of antiarrhythmic agent on the two outcome measures: the proportion of patients in sinus rhythm at the time of study follow up, and mortality.

For each outcome measure, a repeated measures random effects model was used to model the repeated assessments within a study at different time points. In the model, the outcome measure at each time point was weighted by the inverse variance of the outcome measure estimate. The model included treatment, assessment time, and a trial factor to force treatment comparison within the trial. Standard residual diagnostics were used to check for model goodness of fit. Least square means and their 95% confidence intervals (CI) for treatment difference were derived from the fitted models at the median follow up duration. Treatment difference was defined as the absolute difference in the proportion of patients who had experienced the outcome of interest (that is, sinus rhythm or mortality.) To avoid overfitting, effects were considered for classes of drugs rather than for individual drugs. Indicator variables were used for each class of drug, regardless of whether they were used singly or in combination. Two tailed p = 0.05 was considered significant.

Sensitivity analyses

For normal sinus rhythm at follow up, we performed the following sensitivity analyses. Firstly, we conducted subgroup analyses to determine the effectiveness of antiarrhythmic agents in trials that reported follow up of less than one week or at least one week. These analyses were conducted to identify whether any observed effectiveness was transient or sustained. They were also conducted to differentiate use of antiarrhythmic agents for conversion to sinus rhythm from use for maintenance of sinus rhythm. These analyses were done only for comparators where at least three trials were available since the model would not run with one or two trials.

Secondly, we included cohorts of patients who were taking one of the medications under comparison in the main model. These cohorts were extracted from other controlled trials that were included in the meta-analysis but that did not directly compare the medications under comparison. For example, if the main model compared class IA drugs with placebo, we checked the results of this model by including all the cohorts of patients who were taking either class IA drugs or placebo even though these additional cohorts were not part of a trial that directly compared class IA drugs with placebo.
Thirdly, we accounted for variation in trial quality by weighting an outcome on both its precision and its quality. For mortality data, we also performed three sensitivity analyses. Firstly, we included cohorts of patients as described above. Secondly, we assumed that no death was observed for trials that did not report mortality. Thirdly, we accounted for variation in trial quality.

Since amiodarone has several mechanisms of action, we considered the effect of amiodarone versus any other antiarrhythmic agent on sinus rhythm or mortality. Lastly, we considered a large randomised controlled trial that included patients who had recently had atrial fibrillation but did not necessarily have it at the time of enrolment. Although this study considered a slightly different population from the other studies included in this analysis, it was considered because of its large sample size and relatively long duration of follow up.

RESULTS

Literature review

Four hundred twenty eight potentially relevant articles were identified. Reasons for exclusion were non-randomised study design (n = 128); induced atrial fibrillation (n = 3); treatments other than antiarrhythmic agents (n = 34); use of antiarrhythmic agents for prophylaxis alone (n = 56); follow up for < 60 minutes after drug administration (n = 8); lack of data on the proportion of patients in sinus rhythm at study follow up (n = 92); and duplicate publication (n = 16). Ninety one trials met the criteria for inclusion in the analysis.

The appendix (on Heart website only) shows the data abstracted from these articles. There were 43, 29, 47, 1, 51, 21, and 12 trials for placebo, class IA, IC, II, III or IV drugs, and digoxin, respectively. Some trials evaluated more than two drugs or evaluated combinations of drugs. These articles described trials that were conducted in 24 countries and published between 1970 and 2001. The total number of enrolled patients was 8563 (range 18–506). The median duration of follow up was one day (range 0.04–1096, mean (SD) 46 (136) days.) The median proportion of patients in sinus rhythm at follow up was 55% (range 0–100%) and 32% (range 0–90%) for patients receiving active treatment and placebo, respectively. The median survival was 99% (range 55–100%) and 99%
(range 55–100%) for patients receiving active treatment and placebo, respectively. The median quality score was 4 (range 0–7).

**Effect of antiarrhythmic agents on promoting sinus rhythm at follow up**

Compared with placebo, use of the following classes of drugs was associated with significant increases in the proportion of patients who were in sinus rhythm, adjusted for variation in follow up duration (table 1): IA (treatment difference 21.5%, 95% CI 16.3% to 26.8%, p < 0.0001; fig 1; IC (treatment difference 33.1%, 95% CI 23.3% to 42.9%, p < 0.0001; fig 2; III (treatment difference 17.4%, 95% CI 11.5% to 23.3%, p = 0.001; fig 3). Class IC was associated with significant increases in the proportion of patients who were in sinus rhythm at the end of study follow up compared with class IV (treatment difference 43.2%, 95% CI 11.5% to 75.0%, p = 0.03). For each figure, the combined treatment effect was estimated at the median follow up time.

**Effect of antiarrhythmic agents on mortality**

There was no significant difference in mortality between active treatment and placebo for any of the classes of antiarrhythmic drugs considered (table 2).

**Adverse effects of antiarrhythmic agents**

Although we attempted to abstract data describing any adverse effects that were observed in each trial, these were not reported frequently or consistently. Therefore, we were unable to analyse the association between individual classes of drugs and adverse effects.

**Sensitivity analyses**

Among trials that followed up patients for less than seven days, class IC and class III antiarrhythmic drugs were associated with increased sinus rhythm compared with placebo (table 3). Among the same group of trials, no class antiarrhythmic drugs were associated with a significant decrease in mortality.

Among trials that followed up patients for at least seven days, class IA and class III antiarrhythmic drugs were associated with increased sinus rhythm compared with placebo (table 3). Among the same group of trials, there were no significant differences in mortality between the classes of drugs compared.

Among trials that compared amiodarone with other antiarrhythmic drugs, there was no significant difference in sinus rhythm at follow up or in mortality (table 4). When a recent large randomised trial was included in the secondary analysis, the p value was closer to the critical value but was

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Effect of antiarrhythmic agents on mortality in placebo controlled trials</th>
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<tbody>
<tr>
<td>Comparators</td>
<td>Number of trials</td>
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<tr>
<td>IA v placebo</td>
<td>5</td>
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<tr>
<td>IC v placebo</td>
<td>14</td>
</tr>
<tr>
<td>III v placebo</td>
<td>17</td>
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<td>Digoxin v placebo</td>
<td>4</td>
</tr>
<tr>
<td>IA v III</td>
<td>5</td>
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<td>IC v III</td>
<td>8</td>
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<tr>
<td>IC v IV</td>
<td>3</td>
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<tr>
<td>III v digoxin</td>
<td>2</td>
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still not significant (details available from authors). Similar results to those of the primary analysis were obtained when the analysis adjusted for differences in study quality or included study cohorts (details available from authors).

**DISCUSSION**

Compared with placebo, use of several of the classes of drugs considered in this analysis was associated with a significant increase in the proportion of patients who were in sinus rhythm at the time of follow up. However, there were limited data to show whether one class of drug was better than another. Compared with placebo, use of any of the classes of drugs considered in this analysis was not associated with a significant increase or decrease in mortality at the time of follow up. Compared with any other active antiarrhythmic agent, increased or decrease in mortality at the time of follow up. Compared with placebo, use of any of the classes of antiarrhythmic agents was not associated with a significant difference in mortality or quality of life, since the confidence intervals for the effect estimate both overlapped zero. However, the previous analysis considered only the effect of quinidine rather than all class IA drugs.

Controlled trials of class III agents such as amiodarone for ventricular arrhythmias showed small but significant reductions in all cause mortality or arrhythmic death in patients who received treatment rather than the control treatment, in contrast to controlled trials of class IC agents. However, it would be premature to generalise the results of these trials to all patients with atrial fibrillation.

Others have considered the cost effectiveness of treatments for patients with atrial fibrillation. A decision analytical model was used to show that cardioversion followed by aspirin with or without amiodarone was effective and inexpensive. Cardioversion followed by treatment with warfarin and amiodarone was effective but more expensive. The present analysis supports the findings that amiodarone is effective and appropriate in patients with atrial fibrillation.

Another decision analysis had slightly different findings. Of the treatment strategies that were considered, cardioversion followed by repeat cardioversion plus amiodarone on relapse was most cost effective. Our findings support the use of initial treatment with amiodarone rather than delayed treatment, since class III agents are associated with increased sinus rhythm and may be associated with decreased mortality. However, we have not incorporated our results into a decision model since we were unable to show a significant difference in mortality between any class of antiarrhythmic drugs.

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Follow up duration (days)</th>
<th>Number of trials</th>
<th>Treatment difference (%), mean (95% CI)</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Class IA v placebo</td>
<td>7</td>
<td>6</td>
<td>21.1 (15.0 to 27.2)</td>
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<tr>
<td>Class IA v placebo</td>
<td>7</td>
<td>17</td>
<td>31.9 (22.6 to 41.1)</td>
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<tr>
<td>Class III v placebo</td>
<td>7</td>
<td>12</td>
<td>17.3 (9.6 to 25.0)</td>
<td>0.0002</td>
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<tr>
<td>Class III v placebo</td>
<td>7</td>
<td>3</td>
<td>17.6 (3.3 to 31.9)</td>
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<td>Digoxin v placebo</td>
<td>7</td>
<td>4</td>
<td>13.1 (7.2 to 33.3)</td>
<td>0.15</td>
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<td>Class IA v class III</td>
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<td>12.5 (29.7 to 33.3)</td>
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<td>Class IA v class III</td>
<td>7</td>
<td>2</td>
<td>-6.6 (36.7 to 23.5)</td>
<td>0.22</td>
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<tr>
<td>Class IC v class III</td>
<td>7</td>
<td>9</td>
<td>2.5 (-12.7 to 17.2)</td>
<td>0.71</td>
</tr>
</tbody>
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*Other active drugs are digoxin, verapamil, propafenone, quinidine, procainamide, and flecainide.*
A large randomised controlled trial underway is evaluating the use of antiarrhythmic agents by patients with atrial fibrillation. The results of the AFFIRM trial will be reported in 2002. It evaluated the effectiveness of either ventricular rate control or rhythm control with antiarrhythmic agents for total mortality and stroke. All patients received concurrent anticoagulation treatment. Since selection of the type or class of drug was not randomised in this trial, any observed difference between types of antiarrhythmic agents may be confounded by differences in other factors.

Since the present analysis is complex, we will now review the rationale for the inclusion criteria we used and discuss their implications. Firstly, we excluded studies not published in English. Compared with meta-analyses that considered only English articles, those that considered English and non-English articles did not differ with respect to the estimate of benefit of the effectiveness of an intervention. Also, use of such articles would require translation, which was outside of the scope of this study because of the anticipated difficulty in abstracting information about duration of follow up, and rates of dropout and withdrawal. Thus, we relied on citations that were identified by review of English language papers indexed in Medline and of the bibliographies of these articles.

Studies that considered patients with induced atrial fibrillation were excluded since the efficacy of antiarrhythmic agents in patients in an electrophysiology laboratory may not be generalisable to their effectiveness in a less selected population. Treatments other than antiarrhythmic agents, such as ablation, are not widely available. Therefore, the results of studies of these interventions are not generalisable to the population as a whole.

Studies that considered the use of antiarrhythmic agents for prophylaxis alone were also excluded. Since the frequency of the arrhythmia in these patients is unclear, it is difficult to interpret the presence of sinus rhythm at the time of follow up.

Finally, studies that followed up patients for < 60 minutes after drug administration were excluded, since transient conversion may be unsustained. Such transient benefits are unlikely to affect patient morbidity or quality of life.

The effectiveness of each class of drug was expressed as the percentage difference in this analysis. A common alternative approach is to express the effectiveness of each class as an odds ratio. However, odds ratios may be misleading when events are common or when they are observed in a randomised trial rather than a case–control study. Both conditions apply to this analysis. Also, odds ratios do not convey the absolute magnitude of the benefit of treatment.

Limitations of analysis

This analysis has several limitations because of the constraints of the underlying pattern of atrial fibrillation. In our analysis, it was sometimes difficult to determine whether patients who were enrolled in a particular clinical trial had isolated, paroxysmal, persistent, or chronic atrial fibrillation. Despite this, we found consistent results when the data were pooled and analysed in different ways. Thus, we believe that it is unlikely that considering alternative ways of classifying atrial fibrillation would yield different results.

Secondly, the analysis lacked statistical power to detect differences between individual antiarrhythmic agents or to detect small differences between classes of antiarrhythmic agents. Nevertheless, this is the first meta-analysis to discriminate between each class of antiarrhythmic agent and is the largest analysis performed to date of the use of these agents in patients with atrial fibrillation.

Thirdly, the analysis adjusted for variation in follow up duration but not for other parameters of potential interest including use of electrical cardioversion before or after initiation of antiarrhythmic agents, use of transoesophageal echocardiography to identify clot before cardioversion, or clinical characteristics of the patients. Although we attempted to extract such data, the vast majority of the studies analysed did not report them. Therefore, we were unable to evaluate the influence of these variables on sinus rhythm, survival, or other clinical outcomes.

Despite the limitations of the data described above, we believe that this analysis is the most comprehensive assessment to date of the effectiveness of different antiarrhythmic agents in patients with atrial fibrillation. It offers estimates of the effectiveness of different classes of drugs. No other studies have pooled the results of different studies using statistical analysis and adjusted for differences in follow up time. Given the large number of antiarrhythmic agents and large uncertainty about which agent is effective, this meta-analysis is an important advance. Future studies should directly compare specific class III agents and be of sufficient size to determine effectiveness and safety.

In summary, evaluation of the effectiveness of different classes of antiarrhythmic agents continues to be difficult because of inadequate data. The effectiveness estimates derived in this analysis must be interpreted with caution because of the wide variety of classes of drugs considered and of differences in the duration of follow up.

Conclusion

On the basis of a meta-analysis of data from 91 randomised trials of antiarrhythmic agents promoting sinus rhythm in patients with atrial fibrillation, we confirm that class IA, IC, and III drugs are associated with increased sinus rhythm compared with placebo. Class IC drugs are associated with increased sinus rhythm compared with class IV drugs. We are unable to confirm whether any antiarrhythmic class of drug is associated with increased or decreased mortality in this population. Patients, physicians, and policy makers should consider the impact of each class of drug on sinus rhythm, mortality, quality of life, and patient compliance.

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REFERENCES


A 40 year old man was admitted to the emergency department with chest and left shoulder pain for an hour. His admission ECG revealed 3–5 mm ST segment elevation on leads V1–3 and right bundle branch block (RBBB). His previous ECGs were normal. Acute myocardial infarction was diagnosed and thrombolytic treatment initiated. Six hours later, there was no ST segment elevation on leads V1–3 or RBBB on the ECG, and all cardiac enzymes were within normal limits. Echocardiography revealed normal coronary arteries. All ECGs were reviewed and it was decided that the diagnosis of acute myocardial infarction was incorrect. Because of typical ECG findings, an intermittent form of Brugada syndrome was suspected. To confirm the diagnosis (and because of the absence of ajmaline, flecainide, and procainamide) a provocation test with propafenone was performed. The test proved strongly positive for the Brugada syndrome. ECGs of his four family members revealed similar electrocardiographic abnormalities.

While magnetic resonance imaging (MRI) of the heart was normal, MRI of the neck delineated cervical herniation, which might explain the patient’s symptoms.

Brugada syndrome can present with a typical ECG but in some cases the patient can present with concealed or intermittent forms. In the presented case propafenone unmasked ST segment elevation in leads V1–3 and RBBB. The blocking of the sodium channels and β-adrenoceptors contribute to the unmasking effect of propafenone. This case indicates that Brugada syndrome may be confused with AMI, and that propafenone is useful for unmasking the Brugada syndrome ECG pattern.

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Images in Cardiology

Intermittent Brugada syndrome misdiagnosed as acute myocardial infarction and unmasked with propafenone

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