Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation

Freemantle N, Lafuente-Lafuente C, Mitchell S, Eckert L, Reynolds M

CRD summary
The review concluded that all the included antiarrhythmic drugs were efficacious in delaying recurrence of atrial fibrillation. Amiodarone was the most effective in maintaining sinus rhythm. Sotalol and possibly amiodarone increased mortality. Dronedarone possibly decreased serious adverse events and proarrhythmia. The poor quality of many of the included trials and differences across trials limits the reliability of pooled results.

Authors' objectives
To assess the relative efficacy and tolerability of the main antiarrhythmic drugs used for the treatment of atrial fibrillation and atrial flutter.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to 8 April 2009. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that examined the effects of amiodarone, dronedarone, flecainide, propafenone or sotalol versus placebo, no treatment or another antiarrhythmic drug in patients with atrial fibrillation or atrial flutter were eligible for inclusion. Trials that enrolled patients with a follow-up of three months or less, treatment duration of less than 30 days or with atrial fibrillation or atrial flutter three months or less after cardiac surgery were excluded.

The included trials studied amiodarone (200 to 800mg/day), dronedarone (400 to 800mg twice daily), flecainide (100 to 300mg/day), propafenone (450 to 1,200mg daily) and sotalol (80 to 480mg/day). Where reported, the mean age of patients ranged from 49 to 78 years, the proportion of male patients ranged from 35% to 99% and the proportion of patients with structural heart disease varied from zero to 100%. The included trials were published between 1989 and 2009.

Two reviewers independently performed study selection. Discrepancies were resolved by a third reviewer.

Assessment of study quality
Trial quality was assessed on the basis of randomisation, allocation concealment, blinding and completeness of follow-up.

The authors did not state how many reviewers performed quality assessment.

Data extraction
Data were extracted on mortality, stroke, atrial fibrillation recurrence, incidence of serious adverse events (SAEs), treatment withdrawals and proarrhythmia events, and used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

One reviewer performed data extraction, which was checked by a second reviewer.

Methods of synthesis
A random-effects direct meta-analysis was used to calculate pooled Peto odds ratios, together with 95% CIs, on an intention-to-treat basis. A non-linear mixed-treatments meta-analysis was used to perform indirect comparisons. Statistical heterogeneity was derived from the covariance statistic and standard error. When significant heterogeneity was detected, additional analyses that excluded small trials were conducted.

Results of the review
Forty publications were included in the review (approximately 14,413 patients). The quality of the included trials was variable; many trials did not clearly describe blinding or randomisation and some trials had high levels of drop-outs. Trial sample size ranged from 16 to 4,628 patients.

**Direct analysis:** Only results with comparisons of two or more trials are reported here; other results were presented in the review.

There was no statistically significant difference between any of the drugs in terms of mortality. In terms of stroke, there was a statistically significantly lower risk with dronedarone compared with placebo (OR 0.69, 95% CI 0.47 to 0.99; two trials). For atrial fibrillation recurrences, amiodarone had statistically significantly lower rates compared with sotalol (OR 0.47, 95% CI 0.36 to 0.62; five trials). Compared with placebo, all of the drugs studied had statistically significantly greater withdrawals due to adverse events and proarrhythmia events. Amiodarone and flecainide also had a statistically significantly greater risk of serious adverse events compared with placebo. Further results were presented in the review.

**Mixed-treatment analysis:** Sotalol had a statistically significantly higher rate of mortality compared with placebo (OR 3.44, 95% CI 1.02 to 11.59). In trials with more than 100 patients, sotalol had a statistically significantly increased risk of mortality (OR 4.32, 95% CI 1.59 to 11.70) and amiodarone had a marginally statistically significantly increased risk of mortality (OR 2.73, 95% CI 1.00 to 7.41). Dronedarone had a statistically significantly lower risk of stroke compared with placebo (OR 0.69, 95% CI 0.57 to 0.84). All of the drugs studied had statistically significantly reduced atrial fibrillation recurrences compared with placebo. Compared with placebo, there were increased rates of proarrhythmia events with sotalol (OR 6.44, 95% CI 1.03 to 40.24), dronedarone (OR 1.45, 95% CI 1.02 to 2.08) and propafenone (OR 4.06, 95% CI 1.13 to 14.52). There was no significant difference in treatment discontinuations or serious adverse events, but dronedarone, amiodarone and sotalol had statistically significantly greater withdrawals due to adverse events.

There was significant heterogeneity detected in several of the mixed treatment analyses.

**Authors’ conclusions**
All anti-arrhythmic drugs included in the mixed treatment analysis were efficacious in delaying recurrence of atrial fibrillation. Amiodarone appeared to be the most effective in maintaining sinus rhythm. Sotalol and possibly amiodarone increased mortality. Dronedarone possibly decreases the incidence of serious adverse events and proarrhythmia.

**CRD commentary**
Inclusion criteria for the review were clearly defined and several relevant data sources were searched. Publication bias was not assessed and could not be ruled out. Attempts were made to reduce reviewer error and bias during study selection and data extraction; authors did not state whether the same methods were used for quality assessment. Quality assessment was undertaken using basic criteria, which indicated that many of the trials had methodological issues. Trials were combined using appropriate statistical methods. It appeared that statistical heterogeneity was not assessed in the direct analyses. The authors acknowledged high levels of statistical heterogeneity in several of the indirect/mixed-treatment analyses and that some of the outcomes had a low incidence of occurrence and were secondary outcomes in the trials.

The poor quality of many of the included trials and differences across trials limit the reliability of the pooled results.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further large-scale comparative randomised morbidity, mortality and patient-reported outcome trials would be necessary to refine these estimates, particularly for older agents that had a more limited evidence base.

**Funding**
Sanofi-Aventis (manufacturer of dronedarone).
Bibliographic details

PubMedID
21227948

DOI
10.1093/europace/euq450

Original Paper URL
http://europace.oxfordjournals.org/content/13/3/329.abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Amiodarone /adverse effects /analogs & derivatives /therapeutic use; Anti-Arrhythmia Agents /adverse effects /therapeutic use; Atrial Fibrillation /drug therapy; Female; Flecainide /adverse effects /therapeutic use; Humans; Male; Middle Aged; Propafenone /adverse effects /therapeutic use; Randomized Controlled Trials as Topic; Sotalol /adverse effects /therapeutic use; Treatment Outcome

AccessionNumber
12011002034

Date bibliographic record published
10/08/2011

Date abstract record published
29/01/2012

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.