Amiodarone vs sotalol as prophylaxis against atrial fibrillation/flutter after heart surgery: a meta-analysis

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Authors' objectives
To compare the efficiency of sotalol versus amiodarone in preventing the occurrence of atrial fibrillation or flutter (AFF) after coronary artery bypass graft (CABG) surgery.

Searching
MEDLINE was searched from 1985 to 2000 for publications in the English language, using the terms 'coronary artery bypass', 'atrial fibrillation', 'atrial flutter' and 'supraventricular arrhythmias'. The reference lists from the retrieved articles were also examined.

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

Specific interventions included in the review
The prophylactic administration of either sotalol or amiodarone to patients, from between 13 (plus or minus 7) days before undergoing open-heart surgery (CABG with or without valve replacement) to 6 hours after. The included studies reported a range of drug regimens, further details of which are provided in the article. Trials including any other anti-arrhythmic agents were excluded from the review. The control groups received either active placebo or standard treatment.

Participants included in the review
Male or female patients undergoing open heart surgery (CABG with or without valve replacement) were included in the review. The mean ages of the participants were between 57 and 69 years.

Outcomes assessed in the review
Three primary measures of efficacy were evaluated: differences in the incidence of AFF, differences in the numbers of patients requiring discontinuation of the study drug owing to a drug-related adverse event, and differences in the length of stay between the two study groups. The stringency of the diagnosis of atrial fibrillation or flutter varied between the studies.

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
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted on:

the type of study, i.e. primary intervention, intention to treat, use of placebo versus standard treatment, whether double-blinded;

the participants' characteristics, e.g. mean age, and incidence and type of supraventricular arrhythmia.
the form of treatment (sotalol or amiodarone) and the drug regimen, including the start of treatment and the time monitored; the effect of treatment on AFF and adverse drug reactions; and the length of hospitalisation.

A weighted average rate difference (RD), i.e. the difference between the percentage of patients with AFF in the treatment and in the control groups, was calculated for each of the drug trials.

Methods of synthesis
How were the studies combined?
The pooled rate differences were calculated using appropriate methods (see Other Publications of Related Interest nos.1-2.) to derive an average treatment effect. The contribution of each study to the weighted average RD was dependent on the variance of RD for the individual study. The statistical significance of the pooled RD was determined by calculating a z-value. The authors did not report a method for assessing publication bias.

How were differences between studies investigated?
A formal test of homogeneity (see Other Publications of Related Interest no.3) was employed, with a graphical analysis to reinforce the results. The between-study variability, \( t \), was estimated using the method of moments. A sensitivity analysis was performed by carrying out multiple meta-analyses after deleting one study at a time, in order to determine particularly influential studies. Details of other statistical tests for investigating inter-study variability in the different outcome domains were provided in the article.

Results of the review
Ten RCTs were included in the review, of which 5 (n=539) and 5 (n=764) used amiodarone. The intention-to-treat format was reported for only one included study. The formal test of homogeneity found similar results from all of the included studies, and the results were reinforced by the graphical analysis. No adjustment was necessary because the inter-study variability was minimal

The pooled data found that each drug was significantly better than placebo in reducing the incidence of post-operative AFF: the RD was -21.5% (95% confidence interval, CI: -28.3, -14.6, \( p<0.001 \)) for sotalol and -14.1% (95% CI: 20.1, -8.1, \( p<0.001 \)) for amiodarone. While the overall reduction in AFF was greater for sotalol than for amiodarone, this difference was not statistically significant. The results were similar between the two drug groups for adverse drug reactions causing drug termination: the RD was 9.7% (95% CI: 0.086, 19.3) for sotalol and 1.95% (95% CI: -2.5, 11.0) for amiodarone. This difference was significant in the sotalol group, but not in the amiodarone group (\( p=0.12 \)).

No statistically-significant differences were found between amiodarone and sotalol for length of stay: -0.13 days (95% CI: -0.33, 0.07, \( p=0.20 \)) for sotalol and -0.18 days (95% CI: -0.38, 0.02, \( p=0.08 \)) for amiodarone. A subgroup analysis of the 10 studies noted trends in the treatment effect, as influenced by gender distribution and average age of the study population, although these data were not reported in the article. Studies with the highest percentage of men tended to show the smallest treatment effects, while those with older participants showed a trend towards being less responsive to drug treatment.

Cost information
The authors state that studies have reported that AFF can increase length of stay by up to 4.9 days at an increased cost of $10,055 per patient, suggesting that prophylactic treatment for AFF is a cost-effective measure for managing post-operative arrhythmias. Intravenous administration of amiodarone is associated with an increased cost ranging from $500 to $1,000 a day. A 2-day intravenous dose plus oral amiodarone can result in an increased cost of $1,500 to $2,000 per patient. When compared to a 7-day supply of oral sotalol (80 mg) at the average wholesale price of $32.86 per patient, there is a considerable cost difference.
Authors' conclusions
The review suggests that both drug regimens are effective in reducing AFF following heart surgery. The data did not show either drug to be superior in reducing the incidence of post-operative AFF or length of stay. Amiodarone had fewer side-effects requiring drug termination than sotalol, but when compared with each other, no differences were observed.

CRD commentary
The review question and the study selection criteria were clear. The literature search was limited to one source (MEDLINE) and English language publications, so it is possible that studies may have been missed. Apart from checking the reference lists from additional relevant studies, no other means of identifying additional sources were described. The authors did not supply details of how the study selection and data extraction processes were conducted, or on whether or how validity assessments were carried out.

There were occasional typographical errors in the article, e.g. in the reporting of the results of some of the statistical analyses: the frequency of adverse drug reactions for amiodarone were (CI: -0.48, 4.38) in the abstract, (CI: 2.5, 11.0%) in the results section of the article, and (CI: -2.5, 11.%) in table 3. In addition, there were also discrepancies in the spelling of acronyms, e.g. SVT in table 1 instead of SVA, which is very confusing for the reader.

The authors frequently compared the pooled results of amiodarone and sotalol, but these drugs have not been compared in a RCT in this review. Further information on the relative benefits and disadvantages of the two drugs, and indications for their use, were given in the 'Discussion' section of the article.

The authors’ conclusions that sotalol and amiodarone are equally effective is not warranted, as they have not been compared directly in this review.

Implications of the review for practice and research
Practice: The authors state that although either sotalol or amiodarone are equally effective in reducing arrhythmias in patients undergoing heart bypass surgery, amiodarone is more costly than sotalol. As the two drugs each have different metabolic indications for use, these should be balanced against cost considerations before one or the other is employed.

Reviewer's statement: Sotalol and amiodarone have not been compared directly in this review, so the authors cannot conclude that they are equally effective.

Research: The authors state that given the wide degree of variation between the included studies in a number of the key variables, a true comparative study should be undertaken to compare the efficacy of the two drug regimens. Subgroup analysis suggesting that male participants were not as responsive to therapy as female participants, and that the older the patient is, the less responsive they are to therapy, should also benefit from further investigation.

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