Meta-analysis of amiodarone versus beta-blocker as a prophylactic therapy against atrial fibrillation following cardiac surgery

CRD summary
The authors concluded that amiodarone and beta-blockers seemed to have similar efficacy and safety for reducing the risk of postoperative atrial fibrillation. This appeared to have been a well conducted review and the authors' conclusions reflect the evidence presented, but limitations of the evidence base and mean that these conclusions may not be entirely reliable.

Authors' objectives
To compare the efficacy of amiodarone and beta-blockers for preventing postoperative atrial fibrillation.

Searching
MEDLINE, Web of Science and Cochrane Central Register for Controlled Trials (CENTRAL) were searched from January 1990 to October 2011. Search terms were reported. Online clinical trial databases and reference lists of identified studies and three recent conferences were searched to locate further studies.

Study selection
Randomised controlled trials (RCTs) that compared amiodarone and beta-blockers for the prevention of postoperative atrial fibrillation in coronary artery bypass graft surgery, valve replacement or combined surgery were eligible for inclusion. The primary outcome of interest was incidence of postoperative atrial fibrillation; secondary outcomes were also reported. Eligible studies had to have an adequately detailed, published method.

Studies were conducted in the USA, Austria, Lebanon, Iran and Finland. Where reported, age of study patients ranged from 55 to 65 years with the proportion of male patients ranging from 60.1 to 8%. Varying proportions of patients per trial arm had previously been diagnosed with hypertension (range: 48 to 66.7%), diabetes (range: 15 to 45.9%) or chronic obstructive pulmonary disease (range: 1.3 to 17.6%). Half of studies reported all three types of surgery in their samples; the remaining half reported coronary artery bypass graft surgery only or coronary artery bypass graft surgery and valve replacement. Drug regimens varied across the studies. All studies used electrocardiogram monitoring as event-capturing methods, with varying time periods for measurement.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Methodological quality of the studies was assessed using the Jadad scale; maximum scores of 5 indicated the highest quality. Two reviewers independently performed the quality assessment; any disagreements were resolved by consensus.

Data extraction
Data were extracted to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcomes (incidence of atrial fibrillation and postoperative adverse events) and weighted mean differences (WMDs) with 95% confidence intervals for continuous outcomes (length of hospital stay and mean ventricular rate following cardiac surgery). Original data was obtained through contact with study authors.

It appeared as though data might have been extracted independently by two reviewers.

Methods of synthesis
Effect estimates were pooled using the inverse variance method for continuous data and the Mantel-Haenszel method for dichotomous data. Heterogeneity was assessed using $X^2$ and $I^2$. In the presence of significant statistical heterogeneity ($I^2$ greater than 50%) a random-effects model was applied, otherwise a fixed-effect model was used. A range of sensitivity analyses were performed in relation to the incidence of atrial fibrillation. A funnel plot was constructed to assess publication bias. Subgroup analyses were performed for patients receiving different beta-
Results of the review
Six RCTs were included in the review and meta-analysis (1,033 patients). Length of follow-up was either not reported (two trials) or was reported as being one month, the entire hospital stay or time spent in an intensive care unit. Total Jadad scores ranged from 2 to 5; four of the six trials scored a total score of 4 or 5. All six trials reported adequate randomisation. Completeness of follow-up and description of withdrawals were each reported by five trials and four trials reported random sequence generations. Three trials involved double-blinding.

Incidence of atrial fibrillation

No statistically significant difference in the incidence of atrial fibrillation was found between amiodarone and beta-blockers, using fixed-effect (OR 0.81, 95% CI 0.61 to 1.08; six trials) or random-effects models (OR 0.77, 95% CI 0.55 to 1.06; six trials). No significant statistical heterogeneity was indicated ($I^2=34\%$). Sensitivity analyses relating to type of beta-blocker administration, study quality, type of surgery, and use of beta-blockers in the amiodarone groups also demonstrated non-significant results ($I^2$ range 26 to 71%, results reported fully in the paper).

Subgroup analyses revealed a statistically significant lower incidence of postoperative atrial fibrillation with amiodarone, compared with propranolol (OR 0.46, 95% CI 0.27 to 0.78). Results were not statistically significant when amiodarone was compared with bisoprolol or metoprolol.

Other outcomes

No statistically significant differences were shown between amiodarone and beta-blockers for length of hospital stay (WMD -0.05 day, 95% CI -0.64 to 0.54; three trials; $I^2=0\%$), mean ventricular rate following cardiac surgery (WMD -2.31 beats/min, 95% CI -9.98 to 5.36; two trials; $I^2=0\%$) and overall risk of postoperative adverse events (OR 1.00, 95% CI 0.72 to 1.38; three trials; $I^2=0\%$).

Evidence of publication bias was not reportedly found.

Authors’ conclusions

The evidence suggested that amiodarone and beta-blockers had similar efficacy and safety for reducing the risk of postoperative atrial fibrillation.

CRD commentary

The review question was clear and inclusion criteria appeared sufficiently reproducible. Relevant data sources were searched and no language restrictions were applied, which reduced the risk of language bias. Publication bias was not evident from the funnel plot, but the fact that only six small trials were included meant that publication bias could not be ruled out. Efforts were made to minimise the risk of reviewer error and bias during the review process.

Most trials were assessed as high quality using the Jadad Scale and results for individual quality domains were also presented. However, this quality scale has been previously criticised because it does not include assessment of allocation concealment methods (an important potential source of bias), and assessed only the reporting of withdrawals and drop-outs, as opposed to the risk that they might bias trial results. Trial details were adequately reported, which revealed variations in clinical definitions of atrial fibrillation and methods used for atrial fibrillation ascertainment monitoring. Aside from this, methods of synthesis seemed appropriate and levels of statistical heterogeneity were generally low. Sensitivity analyses all revealed similar findings to the main analyses. The authors acknowledged that some relevant data for the secondary outcomes was not available, and pointed out that the review findings related to high risk populations and may not be generalisable to other populations with different baseline risk profiles.

This appeared to have been a well conducted review and the authors’ conclusions reflect the evidence presented, but limitations of the evidence base mean that these conclusions may not be entirely reliable.

Implications of the review for practice and research

Practice: The authors stated (based on the results from only one of the included trials) that clinicians should consider that amiodarone could prevent atrial fibrillation following cardiac bypass grafting surgery in patients with low or very
low ejection fraction levels, prior to prescribing beta-blocker or amiodarone as prophylactic agents.

**Research:** The authors stated that further, prospective research was required to investigate the effects of different beta-blockers and amiodarone on postoperative atrial fibrillation. Future research should also investigate whether beta-blockers and amiodarone might act differently in high-risk patients, with subgroups made according to age and surgery type.

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