Adjunctive antiarrhythmic drug therapy in patients with implantable cardioverter defibrillators: a systematic review

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CRD summary
This review assessed the use of adjunctive anti-arrhythmic drug therapy to reduce the risk of implantable cardioverter defibrillator shock therapies. The authors concluded that only amiodarone appears effective but it cannot be routinely recommended because of potential safety concerns. The review was generally well-conducted, but limited evidence and differences between the studies suggest a more cautious conclusion may be appropriate.

Authors' objectives
To evaluate the efficacy and safety of anti-arrhythmic drug therapy to prevent implantable cardioverter defibrillator (ICD) therapies.

Searching
MEDLINE (1980 to 2006), EMBASE (1980 to 2006) and the Cochrane CENTRAL Register (Issue 1, 2006) were searched; the search terms were reported. In addition, abstracts from meetings of the American Heart Association, American College of Cardiology and the European Society of Cardiology were checked from 2003 to 2006, and the bibliographies of retrieved articles were screened. Ongoing trials were sought through searches of the meta Register of Controlled Trials, ClinicalTrials.gov and the Register of the Center for Clinical Trials and Evidence-Based Healthcare, and experts in the field were contacted for additional published and unpublished studies. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of parallel design and with at least 12 months of follow-up were included in the review.

Specific interventions included in the review
Studies that compared anti-arrhythmic drug therapy to prevent ICD therapies with placebo, beta-blockers or usual care were eligible. Reports comparing a specific class of anti-arrhythmic drug with another were excluded. All included studies used class III anti-arrhythmics. The studies compared sotalol or amiodarone versus beta-blockers (metoprolol, bisoprolol or carvedilol), or compared sotalol, azimilide or dofetilide versus placebo or usual care. In some of the studies comparing anti-arrhythmics with placebo or usual care, a variable percentage of patients in the control arm received beta-blockers.

Participants included in the review
Studies of included patients with ICDs for the primary or secondary prevention of life-threatening ventricular arrhythmias were eligible. The majority of participants had a history of myocardial infarction and were male.

Outcomes assessed in the review
The primary efficacy outcome was the risk of first ICD shock therapy. Secondary efficacy outcomes were appropriate ICD therapy, inappropriate ICD shock therapy, total number of shocks at 12 months, and risk of death or the first ICD (shock) therapy. Safety outcomes included discontinuation of therapy for any reason and new or worsening heart failure.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies, with any disagreements resolved by discussion or by a third reviewer when necessary.

Assessment of study quality
Study quality was assessed on the basis of random allocation, allocation concealment, blinding, completeness of follow-up and intention-to-treat analysis. Two reviewers independently performed the assessment, with any disagreements resolved by discussion or by a third reviewer when necessary.

**Data extraction**
Two reviewers independently extracted the data, with any disagreements resolved by discussion or by a third reviewer when necessary.

**Methods of synthesis**
**How were the studies combined?**
The studies were grouped by comparator (beta-blocker or placebo/usual care). A random-effects model was used to pool data from studies involving different types of anti-arrhythmic drugs, while a fixed-effect model was used for reports of the same type of anti-arrhythmic. Hazard ratios (HRs) with 95% confidence intervals (CIs) were used for most outcomes. The relative risk (RR) and 95% CI were calculated for death or ICD shock therapy and safety outcomes, and mean differences were calculated for continuous efficacy outcomes.

**How were differences between studies investigated?**
Statistical heterogeneity was tested using the chi-squared test and I-squared statistic. The type of anti-arrhythmic drug and rate of concomitant beta-blocker therapy were explored as sources of heterogeneity in a sensitivity analysis.

**Results of the review**
Eight RCTs (n=1,889 patients) were included in the review.

Three studies were considered to be of a high quality; the others were considered to be of low to moderate quality. Three studies reported the method of randomisation, two reported the method of allocation concealment, and seven provided detailed information concerning the loss to follow-up. Four studies were double-blinded.

**Anti-arrhythmic drug therapy versus beta-blockers (3 studies, n=582).**
Anti-arrhythmic drug therapy was associated with a significantly lower risk of ICD shock therapy in the one study that evaluated both amiodarone and sotalol (HR 0.42, 95% CI: 0.19, 0.93, p=0.03); there was evidence of statistical heterogeneity for the different drugs (p=0.05; I-squared 73%). Subgroup analysis by type of anti-arrhythmic drug showed a significant reduction with amiodarone (HR 0.27, 95% CI: 0.14, 0.52, p=0.001), but no significant difference between sotalol and beta-blockers.

Class III anti-arrhythmics were significantly more likely to be discontinued (RR 2.57, 95% CI: 1.32, 5, p=0.006; based on 3 studies); there was a significant increase in the discontinuation rate for amiodarone (RR 3.52, 95% CI: 1.57, 7.97, p=0.002). There was a non significant increase in the risk of new onset or worsening heart failure with anti-arrhythmics compared with beta-blockers (RR 1.44, 95% CI: 0.84, 2.46, p=0.18; based on 2 studies).

**Anti-arrhythmic drug therapy versus placebo or non-anti-arrhythmic therapy (5 studies, n=1,372).**
Compared with control treatment, anti-arrhythmic therapy was associated with a significantly lower risk of all causes of ICD shock therapy (HR 0.67, 95% CI: 0.55, 0.82, p=0.0001).

No significant differences were found for this outcome between azimilide or dofetilide versus placebo. No significant differences were found between the active and placebo groups for discontinuation of therapy or new or worsening heart failure.

**Authors’ conclusions**
Amiodarone reduces the risk of appropriate shock and anti-tachycardia pacing therapies, and appears to be the most effective treatment to reduce ICD shock therapies. However, it cannot be routinely recommended because of potential safety concerns. The benefits of other anti-arrhythmics seems limited to secondary outcomes.
CRD commentary
This review addressed a well-defined question in terms of the patients, interventions, outcomes and study design. Two databases and trial registers were searched and efforts were made to find further published and unpublished studies. No language restrictions were applied, thus limiting the potential for language bias. Publication bias was not evaluated. The authors attempted to minimise bias and errors during the review process, by carrying out the study selection, quality assessment and data extraction processes in duplicate. Significant heterogeneity was found for several analyses but sources of statistical heterogeneity were explored. The numbers of patients involved in the analyses were not consistently reported, which makes it more difficult to assess the strength of the evidence. The review was generally well-conducted, but differences between the studies and the small number of studies and patients available for the primary study outcome suggest a more cautious conclusion may be more appropriate.

Implications of the review for practice and research
Practice: The authors stated that amiodarone cannot be routinely recommended, owing to the poor tolerability and the associated higher risk of developing heart failure.

Research: The authors stated that further RCTs are needed to clarify the usefulness and safety of amiodarone and other class III anti-arrhythmics to prevent ICD shocks.

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