Review: Amiodarone reduces mortality after MI and for congestive heart failure


Question
Using individual patient data, what are the benefits and risks of amiodarone for patients who have congestive heart failure (CHF) or a history of myocardial infarction (MI)?

Data sources
Studies were identified through computerized databases and contact with authors and experts by the Amiodarone Trials Meta-Analysis Investigators (ATMAI).

Study selection
Randomized controlled trials comparing amiodarone with placebo or usual care in patients with CHF or a history of MI were selected.

Data extraction
Data were extracted on inclusion criteria, patient and disease characteristics, dose of amiodarone, type of control (placebo or usual care), duration of the study, and side effects. Main outcomes were all-cause mortality and arrhythmic or sudden death. Individual patient data were extracted or provided by trial investigators.

Main results
8 trials studied 5101 patients who had a history of MI, and 5 trials studied 1452 patients with CHF. All trials included a loading dose and a maintenance dose, both of which varied across studies. The combined mean follow-up was 1.4 years. The mean age of the patients was 61 years, 83% were men, 89% had a history of MI, 21% had nonischemic cardiomyopathy, 18% had diabetes, and 42% had ventricular tachycardia. The mean left ventricular ejection fraction was 31%. 29% of patients discontinued amiodarone early.

For all studies using intention-to-treat meta-analysis, the all-cause mortality rate was lower in the amiodarone group than in the control group ($P = 0.03$), as was the rate of arrhythmic or sudden death ($P < 0.001$) (Table). Heterogeneity was noted with differences in treatment effect among the individual trials. Subgroup analysis found no differences in benefit with amiodarone therapy among subgroups defined by sex, left ventricular ejection fraction, history of MI, type of control (placebo or usual care), or ventricular premature depolarization or ventricular tachycardia.

Conclusion
Amiodarone leads to a modest reduction in all-cause mortality, death from arrhythmia, or sudden death in patients who have congestive heart failure or a history of myocardial infarction.

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Amiodarone vs control for high-risk patients (congestive heart failure or history of myocardial infarction)*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Weighted amiodarone</th>
<th>Weighted control</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>10.9%/y</td>
<td>12.3%/y</td>
<td>72</td>
</tr>
<tr>
<td>Arrhythmic or sudden death</td>
<td>4.0%/y</td>
<td>5.7%/y</td>
<td>77</td>
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</tbody>
</table>

*Abbreviation defined in Glossary.

Several effective treatments, including β antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor antagonists, are available to reduce mortality in patients with CHF or a history of MI (1, 2). However, many of these patients are still at increased risk for death caused by ventricular arrhythmia. Class I antiarrhythmic agents and β-blockers (a class III potassium channel blockers) have been shown to be ineffective in these patients (3, 4). Amiodarone, a drug with a complex pharmacologic profile that includes antiarrhythmic properties, has been studied in patients with CHF and recent MI; > 12 studies have reported inconclusive results.

The ATMAI trial used individual patient data from 8 studies of patients after MI and 5 studies of patients with CHF. Sim and colleagues used published summary data of the same 13 studies and 2 additional studies on patients who had cardiac arrest. These 2 approaches provide the similar overall conclusion that amiodarone modestly reduces all-cause mortality about 10% to 19%.

Major adverse drug effects from 6 double-blind, placebo-controlled studies were analyzed in the ATMAI study. Compared with patients receiving placebo, patients receiving amiodarone had an increased risk for hypothyroidism (odds ratio [OR] 7.3), hyperthyroidism (OR 2.5), pulmonary infiltrates (OR 1.1), bradycardia (OR 2.6), and liver dysfunction (OR 2.7). At the end of 2 years, more patients in the amiodarone group than in the control group had permanently discontinued the study medications (41% vs 27%), primarily because of adverse effects.

When sudden death was used as the outcome, both meta-analyses found an approximately 30% relative risk reduction, suggesting that amiodarone is effective in preventing arrhythmia-related deaths. Sim and colleagues also reported no difference in treatment effect among patients with CHF or a history of MI or cardiac arrest. A nonsignificant trend was shown toward larger benefits in trials that required documentation of arrhythmia. The placebo-controlled trials showed fewer benefits with amiodarone than the usual-care controlled trials. This suggests that the larger benefits seen with usual care may simply be a reflection of the harmful arrhythmic effects of other drugs rather than of amiodarone efficacy. Unfortunately, the drugs used in the usual-care controls were not reported in detail in the primary studies.

The ability to access the original individual patient data and the collaboration of study investigators allowed the ATMAI group to harmonize disparate data and do additional analyses. Of the 16 subgroup analyses, a large fraction of the studies. (continued on page 113)