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FROM THE FAMILY PRACTICE INQUIRIES NETWORK

Do antiarrhythmics prevent sudden death in patients with heart failure?

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EVIDENCE-BASED ANSWER

Beta-blockers (class II antiarrhythmics) reduce sudden death and total mortality in patients with heart failure (strength of recommendation [SOR]: **A,** based on systematic reviews of randomized controlled trials). Amiodarone (class III) may reduce sudden death in heart failure (SOR: **B,** extrapolation from randomized controlled trials), but evidence is weak that it reduces total mortality, and it has significant side effects. Class I and other class III antiarrhythmic agents appear cause an increase in mortality due to sudden death in heart failure (SOR: **B,** extrapolations from randomized controlled trials).

EVIDENCE SUMMARY

Antiarrhythmic agents have been studied in patients with heart failure because these persons have a high incidence of sudden death, presumably from ventricular arrhythmias. Although the implantable defibrillator is an alternative antiarrhythmic device that may be preferred for some patients, we restricted our review to pharmacologic antiarrhythmics.

The beta-blockers bisoprolol, carvedilol, and metoprolol[1-3] were studied in large randomized controlled trials. The relative risk reduction (RRR) for sudden death ranged from 10% to 52% in the larger trials and 30% to 39% in meta-analyses.[1-4] The absolute risk reduction (ARR) was about 2% to 3% per year for sudden death and 3% to 5% for total mortality (number needed to treat=20–33 per year).

These beta-blockers were well-tolerated, even in class IV New York Heart Association patients, and improved other endpoints. Although we cannot say whether the benefits are a class effect, they were seen with both beta-1 selective and nonselective agents.

Amiodarone was studied in 2 large randomized controlled trials enrolling patients with heart failure, in trials that

included patients with or without heart failure at high risk for sudden death (usually post-myocardial infarction or with complex ventricular arrhythmias), and in meta-analyses.[5-8] The largest randomized controlled trial in heart failure showed a significant ARR of 2.9% for sudden death,[5] but was unblinded. The largest placebo-controlled trial in heart failure failed to detect a significant decrease in sudden death.[6]

Meta-analyses, weakened by heterogeneity and the inclusion of patients without heart failure, detected a significant 21% to 25% RRR for sudden death,[7,8] and an ARR of 2% to 3% per year. The pooled data from the placebo-controlled heart failure trials showed nonsignificant trends: 1.6% per year ARR for sudden death, 0.6% per year for total mortality.

These possible benefits must be balanced against the risk of harm from amiodarone, including excess rates of pulmonary infiltrate (1.1% per year), thyroid dysfunction (6.8% per year), liver enzyme abnormalities (0.6% per year), neuropathy (0.3% per year), and bradycardia (1.6% per year), as well as a discontinuation rate of 41% compared with 27% for placebo.[7] No evidence suggested that use of amiodarone in patients with heart failure increased mortality.

Class I antiarrhythmics and other class III agents have not been studied in heart failure trials, but were associated with increased mortality in studies of patients at high risk for ventricular arrhythmia,[9,10] including patients with left ventricular dysfunction. Because this increase in mortality is thought to be due to proarrhythmic properties of the drugs, further trials in heart failure patients are unlikely to occur.

RECOMMENDATIONS FROM OTHERS

American College of Cardiology/American Heart Association (ACC/AHA),[11] European Society of Cardiology (ESC),[12] and Heart Failure Society of America (HFSA) guidelines[13] address heart failure. ACC/AHA and ESC reports specifically mention that beta-blockers reduce sudden death. Both strongly support the use of beta-blockers in patients with heart failure.

ACC/AHA finds “conflicting evidence and/or a divergence of opinion about the usefulness/ efficacy” of amiodarone to prevent sudden death and advises: “routine use of amiodarone to prevent sudden death is not recommended.” The ESC and HFSA also recommend against routine use of amiodarone.

All 3 guidelines, however, state that for the control of symptomatic arrhythmias in heart failure, amiodarone is the antiarrhythmic agent of choice. All 3 also recommend not using class I or other class III agents in heart failure.

CLINICAL COMMENTARY

Beta-blockers reduce mortality in patients with heart failure

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Numerous well-controlled clinical trials have conclusively demonstrated that beta-blockers reduce morbidity and mortality (including sudden death) in patients with systolic heart failure. They are considered disease-modifying agents and their use is strongly encouraged. Beta-blocker therapy must be initiated using low doses and only when patients are hemo-dynamically stable, with gradual dose titrations to prevent acute decompensation.

Evidence for amiodarone shows some reduction in sudden death, but these data are less compelling. Moreover, adverse effects and drug interactions complicate long-term amiodarone use. Use of class I (eg, flecainide, procainamide, propafenone) and other class III (sotalol) anti-arrhythmics to reduce sudden death is discouraged.

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