Clinical Questions #5

Editor's note: This is the fifth installment in a series of "Clinical Questions." Readers are presented with a case and clinical question. An evidence-based answer is provided on a later page. The answer includes how the evidence was found and evaluated.

Maintenance of normal sinus rhythm after cardioversion: Is amiodarone better than placebo?

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Patient

A 79-year-old male with ischemic cardiomyopathy (ejection fraction of 40%) and hypertension presents with a left cerebellar and left thalamic infarct secondary to new onset atrial fibrillation with rapid ventricular response. He is cardioverted to normal sinus rhythm because of rapid ventricular response and hypotension.

Clinical Question

In a patient with atrial fibrillation and ischemic cardiomyopathy in sinus rhythm after cardioversion, does amiodarone versus placebo improve maintenance of normal sinus rhythm?

How and where could you locate evidence to answer this question?

How would you treat this patient?

Turn the page for one possible approach.

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Suggested Approach for Clinical Question #5

Search Strategy

1. Cochrane Database of Systematic Reviews (2nd Quarter 2005) using OVID interface:
   a. "amiodarone or cordarone or pacerone"
   b. "atrial fibrillation or afib"
   c. combine (a) and (b)
   d. One match. This was only a protocol, so the review was not yet complete
   Lafuente-Lafuente, C. Mouly, et al. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. [Protocol]
2. Search repeated in Database of Abstracts of Reviews of Effects (DARE) and ACP Journal Club using the Ovid Interface:
   a. Limited to therapeutics
   b. 28 studies—one applicable:
      i. Amiodarone maintained sinus rhythm better than did sotalol or placebo in atrial fibrillation, but adverse effects were more frequent. (Review of Kochiadakis 2000.)
3. Search all years of Medline using Ovid Interface (1966 to June Week 5 2005):
   a. "amiodarone" (MeSH heading)
   b. "atrial fibrillation" (MeSH heading)
   c. "cardiover$" (keyword)
   d. Combine (a) and (b) and (c) limited to human and English
   e. Limit (d) to "therapy (specificity)" under Clinical Queries
   f. 35 studies—2 pertained to the question:
      i. Singh BN, et al. Sotalol amiodarone atrial fibrillation efficacy trial (SAFE-T).
      ii. Kochiadakis GE, et al. Low dose amiodarone and sotalol in the treatment of recurrent, symptomatic atrial fibrillation: a comparative, placebo controlled study.

Study Characteristics

Study	Singh	Kochiadakis
Study type	Randomized, double-blind, placebo-controlled	Randomized, single-blind, placebo-controlled
Patients	665 patients on anti-coagulation with documented atrial fibrillation for >72 hours	186 patients with recurrent, symptomatic atrial fibrillation (paroxysmal or chronic) and successful cardioversion
Intervention	Amiodarone, sotalol, or placebo*	Low dose Amiodarone (200 mg/day), sotalol, or placebo
Primary End Points	Time to recurrence of atrial fibrillation if cardioversion successful	Recurrence of atrial fibrillation or side effects

* DC cardioversion attempted if in persistent atrial fibrillation 28 days after study drug administered. If DC cardioversion unsuccessful on D28, study drug withdrawn, and the patients followed for 1 year. D28 considered Time 0.

Validity of Evidence

Singh

- Properly performed stratified block randomization.
- Follow-up was long enough—between 12 and 54 months.
- Moderate loss to follow-up with only 84% of subjects completing at least 1 year of the study.
- Intention-to-treat analysis was used.
- The study was "double-blinded" and properly placebo controlled.
- The 3 groups were treated equally with similar follow-up.
- The groups were similar at the start of the study.
- Overall, this is a good quality study. Deficiencies include the relatively high dropout rate and unclear use of other interventions such as rate-controlling medications.

Kochiadakis

- Properly randomized.
- Follow-up was long enough—between 21.6 and 22.3 months.
- Authors appear to use intention-to-treat analysis.
- Only patients were blinded.
- The groups were similar at the start of the study.
- The 3 groups were treated equally with routine follow-up visits.
- Overall, this is a good quality study. One deficiency is single-blinding.

Study Results

Study	Singh*	Kochiadakis†
Recurrence in amiodarone group	35%	48%
Recurrence in placebo group	82%	88%
Relative risk reduction	58% (95% CI, 48-66%)	46% (95% CI, 29 –59%)
Number needed to treat	2.1 patients (95% CI 2-3)	2.4 patients (95% CI 2-4)

* Results at 1 year in patients with successful cardioversion
† Results at mean follow-up of 22 months

Singh

There were 13 deaths in the amiodarone group versus 3 deaths in the placebo group. After adjustment for the duration of follow-up, the hazard ratio was not statistically significant for the amiodarone group versus placebo.

Kochiadakis

Twenty three percent developed significant side effects on amiodarone including symptomatic bradycardia, hypothyroidism, hyperthyroidism, ataxia, gastrointestinal discomfort, nausea, photosensitivity, and ophthalmic problems.

Applying the Evidence to the Patient

- Our patient may have been more ill than those in the studies since he was treated as an inpatient and his heart rate was poorly controlled prior to cardioversion. However, some patients in the studies did have decreased ejection fractions and coronary artery disease.
- The treatment is feasible in our hospital setting.
- Potential benefits of amiodarone include maintenance of sinus rhythm. Our patient became hemodynamically unstable when in atrial fibrillarion.
- Potential harms include toxicities of amiodarone such as hyper/hypothyroidism, lung toxicity, liver function test abnormalities, bradycardia, photosensitivity, and corneal deposits. There may even be a trend toward increased mortality as seen in the Singh study.

Summary

These 2 well-done studies demonstrated a similar dramatic decrease in the recurrence of atrial fibrillation with amiodarone compared to placebo in patients after cardioversion. There were some weaknesses of the studies including a high dropout rate and unclear use of other interventions in the Singh study. Single-blinding was a weakness in the Kochiadakis study. Amiodarone showed an increase in hypo- and hyperthyroidism, gastrointestinal discomfort, and also has many other known toxicities. There was also a troubling trend toward increased mortality in the Singh study. We would expect to see similar results in our patient.

Bottom Line

Amiodarone is superior to placebo in maintaining normal sinus rhythm after cardioversion. However, one must weigh its benefits against its potential toxicities. The concerning trend toward increased mortality needs to be further investigated. We would prescribe amiodarone to our patient. His risk of atrial fibrillation with recurrent hypotension outweighs the potential risks of amiodarone.

Bibliography

1. Singh BN, Reda DJ, Tang XC, et al. Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) Investigators. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med*. 2005;352(18):1861-1872.
2. Kochiadakis GE, Igoumenidis NE, Marketou ME, Kaleboubas M, Simantirakis EN, Vardas PE. Low dose amiodarone and sotalol in the treatment of recurrent, symptomatic atrial fibrillation: a comparative, placebo-controlled study. *Heart*. 2000;84:251-257.