Critical Review Form
Meta-analysis

Chevalier P, Durand-Dubief A, Burri H, Cucherat M, Kirkorian G, Touboul P. Amiodarone versus placebo and class Ic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. J Am Coll Cardiol. 2003 Jan 15;41(2):255-62.

Objectives: **"to clarify by meta-analysis the role of amiodarone in the cardioversion of recent-onset AF [atrial fibrillation]." (p. 255)**

Methods: **This systematic review and meta-analysis sought to identify prospective, randomized controlled trials in which amiodarone was compared to placebo or a class Ic drug for the cardioversion of recent-onset (1 week or less) AF. Trials evaluating patients with atrial flutter or post-operative AF were excluded. Medline, EMBASE, and the Cochrane Controlled Trials Register were searched (last conducted on October 18, 2001) with no language limit for relevant articles. The reference lists of selected articles and of related review articles were searched for additional studies. Authors also searched abstracts of relevant scientific meetings (the American Heart Association, the American College of Cardiology, and the European Society of Cardiology) and contacted drug manufacturers.**

The primary endpoint being evaluated was cardioversion by 24 hours after drug administration. Secondary endpoints were cardioversion at 1 to 2 hours, 3 to 5 hours, and 6 to 8 hours, mortality, "proarrhythmia," and adverse events (including bradycardia, hypotension, and heart failure).

The combined literature search yielded 79 articles, from which 69 were excluded. This left 10 total studies included in the analysis, of which 6 compared amiodarone to placebo (n = 595) and 7 compared amiodarone with a class Ic drug (n = 807, of which 579 were included in the analysis). Three of the studies overlapped, comparing amiodarone with both placebo and class Ic drugs.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes. Chemical cardioversion is frequently used for patients with recent-onset AF, and in particular has been recommended by some groups for ED management of AF of duration < 48 hours (see Aggressive Ottawa Protocol and prior journal club on this topic).
2.	Was the search for relevant studies detailed and exhaustive?	Yes. The authors searched Medline, EMBASE and Cochrane, as well as conference abstracts. They did not search the gray literature.
3.	Were the primary studies of high methodological	Uncertain. The authors did nothing to assess the quality of studies being included. Several tools exist to assist

	quality?	with quality assessment, particularly for systematic reviews of randomized, controlled trials, including the two-part tool described in section 8.5 of the Cochrane Handbook (Higgins 2011), which looks at six specific domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential threats to validity.
4.	Were the assessments of the included studies reproducible?	See above. No assessment was performed.
II.	***What are the results?***	
1.	What are the overall results of the study?	Cardioversion: Amiodarone showed greater efficacy compared to placebo at 6 to 8 hours and at 24 hours, but no efficacy at 1 to 2 hours: • 6-8 hr: RR 1.23, 95% CI 1.03 to 1.47 • 24 h: RR 1.44, 95% CI 1.24 to 1.66 • 1-2 h: RR 1.23, 95% CI 0.77 to 1.96 Class Ic drugs were more effective than amiodarone at 1 to 2 hours, 3 to 5 hours, and 6 to 8 hours, but had similar efficacy at 24 hours: • 1-2 h: RR 0.35, 95% CI 0.24 to 0.50 • 3-5 h: RR 0.44, 95% CI 0.31 to 0.61 • 6-8 h: RR 0.57, 95% CI 0.57 to 0.80 • 24 h: RR 0.95, 95% CI 0.83 to 1.09. Adverse effects: There were no deaths in any of the trials. Nonsustained ventricular tachycardia was reported in 3 patients: 2 who received amiodarone and 1 who received propafenone. One episode of sustained ventricular tachycardia was reported in a patient receiving placebo.
2.	How precise are the results?	See above.
3.	Were the results similar from study to study?	The authors report that there was significant heterogeneity for the results, but only report measures for some outcomes. The reported p-values do not consistently suggest a high degree of heterogeneity. For amiodarone vs. placebo, at 1-2 hours they report a Cochrane's Q p-value of 0.55; at 24 hours the p-value was < 0.001. For the comparison of amiodarone to class Ic drugs at 1-2 hours, $p < 0.001$; at 24 hours, $p = 0.50$.
III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to	This meta-analysis seems to suggest that administration of amiodarone does not result in early conversion of

	the care of my patients?	recent-onset AF to a normal sinus rhythm when compared to placebo, and hence may be a poor choice when attempting to convert a patient in the ED with the hopes of discharging them home. Class Ic agents (e.g. flecainide, encainide, and propafenone) seem more efficacious at earlier timeframes, though by 24 hours they are no better than amiodarone. Unfortunately, the failure on the part of the authors to assess the quality of the included studies makes it difficult to rate this evidence, and hence makes it difficult to use this information to direct patient care. It is also unclear whether any of these patients were recruited from the ED, which may affect the studies' external validity.
2.	Were all patient important outcomes considered?	Yes. The authors considered the ability of amiodarone to convert recent-onset AF to normal sinus rhythm, compared to placebo and class Ic antiarrhythmics, at a variety of time periods. They also looked at several key adverse effects from antiarrhythmic drug administration. They did not look at studies comparing the efficacy of amiodarone to procainamide, a class Ia antiarrhythmic that has been more frequently recommended for recent-onset AF.
3.	Are the benefits worth the costs and potential risks?	Uncertain. This study suggests that amiodarone is no more effective at converting recent-onset AF to sinus rhythm within 8 hours than placebo, which would prohibit its use in early cardioversion in the ED. Unfortunately, the authors did not provide a quality assessment of the included studies and did not provide any information regarding inclusion of ED patients in the study. Additionally, this study did not look at the efficacy of procainamide in early cardioversion of AF, which some research has suggested is much more efficacious.

Limitations:

1. **The authors provide no quality assessment of the articles included in the meta-analysis. Several tools exist to perform such assessments, including that found in section 8.5 of the Cochrane Handbook (Higgins 2011).**

2. **Despite reported including criteria, the authors elected to include one study of patients with AF duration up to 2 weeks and an additional study that included small number of patients with postoperative AF. These *ad hoc* protocol violations undermine the rigorousness of the literature search performed.**

3. **The authors provide very little clinical information regarding the included studies, including failure to detail the practice setting (external validity).**

4. **There was a great deal of clinical heterogeneity noted between studies, with varying doses and routes of amiodarone administration (2 of 10 studies involved oral administration).**

5. **Despite the degree of heterogeneity noted between studies (though not reported), the authors chose to report pooled results based on a fixed effects model. They do report that random effects models were also conducted with the same results, but do not provide these results.**

Bottom Line:

This systematic review and meta-analysis evaluating the efficacy of amiodarone for cardioversion of recent-onset (one week or less) AF revealed no benefit from amiodarone administration compared to placebo at 1-2 hours after infusion. There was a significantly higher rate of cardioversion at 6-8 hours and 24 hours, but class Ic drugs resulted in significantly higher rates of cardioversion compared to amiodarone at all times up to 24 hours, with similar rates seen at 24 hours. This data suggests little benefit from amiodarone administration for recent-onset AF in the ED if the goal is to prevent hospital admission. None of the included studies compared amiodarone to procainamide, which has demonstrated fairly high rates of cardioversion of AF in the ED setting.