Critical Review Form
Therapy

PGY-1

HYPERLINK "http://pmid.us/7977118"Goldenberg IF, Lewis WR, Dias VC, Heywood JT, Pedersen WR. Intravenous diltiazem for the treatment of patients with atrial fibrillation or flutter and moderate to severe congestive heart failure. Am J Cardiol. 1994 Nov 1;74(9):884-9.

Objectives: **"to assess the safety and efficacy of intravenous diltiazem in patients with atrial fibrillation or flutter and moderate to severe congestive heart failure." (p. 884)**

Methods: **This multicenter, randomized, double-blind, placebo-controlled trial was conducted at 8 tertiary care hospitals from July 1987 to October 1990. Patients with spontaneous atrial fibrillation with a ventricular rate ≥ 120 beats per minute for at least 15 minutes with NYHA Class III or IV congestive heart failure, with evidence of pulmonary edema on examination or chest x-ray, were eligible for inclusion.**

Patients were randomized to receive either intravenous diltiazem (0.25 mg/kg) or placebo as an initial treatment (drug period I). Response to treatment was defined as a reduction in ventricular rate to less than 100 beats per minute, reduction in ventricular rate ≥ 20% from baseline, or conversion to sinus rhythm. Patients who did not respond after 15 minutes were them given IV diltiazem (0.35 mg/kg) or placebo (drug period II). Patients who still did not respond after an additional 15 minutes were then unblinded; placebo nonresponders were given IV diltiazem (0.25 mg/kg) (drug period III), followed by an additional dose (0.35 mg/kg) if they continued to fail to respond after a further 15 minutes (drug period IV). Patients who responded could be started on an open-label infusion of IV diltiazem (10-15 mg/hr) for 4 hours, at the investigator's discretion.

There were 37 patients enrolled during the study period, of whom 22 were randomized to receive diltiazem and 15 to receive placebo. Atrial fibrillation was seen in 78% of patients and atrial flutter in 22%. The mean ejection fraction was 36% (range 10 to 80).

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. The authors report that patients were randomized to receive placebo or diltiazem. They do not report the randomization scheme (e.g. 1:1, block randomization, permuted blocks).

2.	Was allocation concealed? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Uncertain. The authors provide no information regarding sequence generation or methods to maintain allocation concealment.
3.	Were patients analyzed in the groups to which they were randomized?	Likely yes. The authors do not specifically mention the use of an intention to treat analysis, but make no mention of crossover between groups.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. While patients were similar with respect to age, weight, history of congestive heart failure, baseline heart rate, and history of valvular disease, patients in the diltiazem group had higher mean baseline ejection fraction (39% vs. 32%), were more likely to have pulmonary congestion on chest x-ray (82% vs. 67%), and were less likely to have had cardiac surgery in the previous 2 weeks (23% vs. 40%). The authors do not report additional medical comorbidities or baseline blood pressure.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Uncertain. While the authors call this a "double blind study," they do not specify who was blinded or how this was achieved.
2.	Were clinicians aware of group allocation?	See above.
3.	Were outcome assessors aware of group allocation?	Uncertain. There is no specific mention of blinding of outcome assessors.
4.	Was follow-up complete?	Yes. All outcomes were measured during the index visit, hence outcomes were available for all patients enrolled.
II.	**What are the results ?**	
1.	How large was the treatment effect?	● During drug period I of the blinded period, more patients in the diltiazem group had a therapeutic response vs. the placebo group: 82% vs. 0%, $p < 0.001$. ○ Of 4 patients in the diltiazem group who did not respond, one was inadvertently not given any additional study drug; the other 3 responded to a 2nd dose of IV diltiazem (drug period II).

		○ None in the placebo group had a response to a 2nd dose of placebo during drug period II. ● During the open label part of the study (drug period III), all 15 placebo group patients received IV diltiazem, with 13 designated as responsive to this treatment; the remaining 2 patients responded to a 2nd dose of IV diltiazem. ● All 36 responders achieved a > 20% decrease in HR, while 17 achieved a HR < 100 beats/min. ● Mean blood pressure was somewhat lower in the diltiazem group at the end of period I compared to the placebo group (118 ± 5 vs. 127 ± 6), as was diastolic blood pressure (69 ± 3 vs. 79 ± 5). ○ Hypotension occurred in 2 patients in the diltiazem group (9%) and was symptomatic in one patient. No patient in the placebo group had an adverse event in period I. ○ There was no difference in the incidence of hypotension between those with an EF < 25% and those with an EF > 25%. ● No patient developed worsening congestive heart failure due to receipt of diltiazem.
2.	How precise was the estimate of the treatment effect?	See above. This study did not report actual effect sizes or associated confidence intervals.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	No. This study was conducted in 1995; the pharmacologic approach to both the chronic and acute management of CHF and atrial dysrhythmias has changed drastically in the interim, limiting the generalizability of these results to the modern patient (external validity).
2.	Were all clinically important outcomes considered?	Yes. While much of the comparison seems obvious and unnecessary (i.e. differences in rate control between diltiazem and placebo), the authors do consider effects on blood pressure and heart failure (though they do not appear to assess objective measures of heart failure in their comparisons).
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While this study confirms that diltiazem is effective as a rate control agent for atrial fibrillation in patients with CHF, and suggests that it does not worsen heart failure symptoms, this was a very small study that did not compare diltiazem with other pharmacologic options (e.g. metoprolol and amiodarone), nor does it a provide a sufficiently

		robust examination of the effects of diltiazem on congestive heart failure throughout hospitalization for these patients.

Limitations:

1. **Several components of the CONSORT statement checklist for reporting of randomized controlled trials were not included in this article (understandable as this article preceded CONSORT), including:**
    a. **Primary outcome**
    b. **Method of random sequence generation**
    c. **Methods to maintain allocation concealment**
    d. **Methods of blinding**
2. **There were 10 patients (over a quarter of all those enrolled) with an EF > 40%.**
3. **The authors do not report actual effect sizes or associated confidence intervals.**
4. **The study was conducted in 1995; changes in the pharmacologic management of atrial fibrillation and CHF may affect these results (external validity).**

Bottom Line:

This small randomized controlled trial found that among patients with CHF being treated for atrial fibrillation with a ventricular rate ≥ 120 beats per minute, diltiazem is both an effective and safe option for rate control. Given the small size of the study, lack of comparison to additional pharmacologic options, and changes in management of both conditions over the subsequent 30+ years, these findings should be considered cautiously and used in conjunction larger, more recent studies.