EVMS EM JC CRITICAL REVIEW FORM: THERAPY ARTICLES

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Citation: Fromm, et al. Diltiazem vs. Metoprolol in the Management of Atrial Fibrillation or Flutter with Rapid Ventricular Rate in the Emergency Department. *Pharmacology in Emergency Medicine*. J Emerg Med 49 (2): 175 – 182.

Study Objective: To compare the effectiveness of diltiazem with metoprolol for rate control of Atrial Fibrillation/Flutter (AFF) in the Emergency Department.

Study Methodology: A prospective, randomized double-blind convenience sample of adult patients presenting with rapid AFF to a single-site urban adult ED teaching hospital with an annual patient volume of >120,000 patients. The patient's systolic blood pressure, diastolic BP, and heart rates were monitored for 30 minutes after administration of the respective medication. Eligible patients had a 12-lead electrocardiogram (ECG) showing atrial fibrillation or atrial flutter with a ventricular rate of 120 beats per minute (bpm) and a systolic blood pressure (SBP) of 90 mm Hg. Patients were excluded if they had any of the following: SBP < 90 mm Hg, ventricular rate > 220 bpm, QRS > 0.100 s, second- or third-degree atrioventricular (AV) block, temperature > 38.0 C, acute ST elevation myocardial infarction, history of Class IV heart failure, active wheezing with a history of asthma or chronic obstructive pulmonary disease (COPD), if there was prehospital administration of diltiazem or any other AV nodal blocking agent, a history of cocaine or methamphetamine use in the 24 hours before arrival, a history of allergic reaction to diltiazem or metoprolol, a history of sick sinus or pre-excitation syndrome, a history of anemia with hemoglobin < 11.0 g/dL, pregnancy, or breastfeeding.

GUIDE	COMMENTS
I. Are the results valid?	
A. Did experimental and control groups begin the study with a similar prognosis?	This was a direct comparison between two different medications and therefore, there is not a control group. However, both the diltiazem and metoprolol groups had the same initial diagnosis, inclusion/exclusion criteria, and the demographics/characteristics that were included in Table 1 were not statistically different.
1. Were patients randomized?	Yes, patients were randomized. Upon enrollment, patients were randomly assigned in a 1:1 ratio to receive either diltiazem or metoprolol, which was performed using computer-generated randomization by one investigator and then given to pharmacy investigators. The study drug was then released in a locked tackle box coded in number sequence to correspond with the randomization list. The pharmacists also prepared the study drug in a blinded fashion in conjunction with this list. The study medications were packaged in identical-appearing dispensing kits and syringes with the same total volume of

	drug and each physician, nurse, and patient were studied to the drug. Further escalation doses were also prepared and administered in a blinded fashion.
2. Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Randomization was performed by one investigator and then the other investigators acted upon the list. Each party was blind to the other's actions. Total volume within each syringe was adjusted with normal saline by an ED pharmacist to a total of 10 mL to disguise and maintain blinding. I do not believe it was possible to subvert this.
3. Were patients analyzed in the groups to which they were randomized?	Yes, for the most part. Patients were randomized and then analyzed in their respective groups. 2 patients (1 for each group) were not analyzed, as one became uncooperative and left the study and then another became hypotensive within 5 minutes of administration of the study drug. An argument could be made that these individuals should have been included in an intention-to-treat analysis since in such a small N 1 patient represents 4% of the group.
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	Patients in the treatment groups were similar in mean age, those receiving pre-treatment adenosine, baseline SBP, baseline DBP, baseline HR, sex, age, alcohol use, medical history, and comorbid conditions: COPD, pre-existing Afib, thyroid disease, DM, and…new onset Afib. Potentially significant but not included: time in AF, CKD, Hx. CHF, HTN (all RF's for worse outcomes in AF).
5. Were patients aware of group allocation?	No, they were blinded to the study drug and their group allocation.
6. Were clinicians aware of group allocation?	No, physicians and nurses were blinded to which drug the patient was receiving.
7. Were outcome assessors aware of group allocation?	It does not explicitly say – based on the safety-monitoring team's ability to observe that significantly more patients in one study group were meeting the primary outcome, I would say they were not blinded; however, an independent biostatistician was blinded and confirmed the findings.
8. Was follow-up complete?	Follow-up was complete in as far as treatment in the ED. Patients were not followed after admission, discharge, or in regard to morbidity, mortality, or length of stay in the hospital.
What are the results?	"Diltiazem was more effective than metoprolol in achieving rate control in ED patients with AFF at all time points within 30 min and did so with no increased incidence of adverse effects."
1. How large was the treatment effect?	The hazard ratio, which they are using as a comparison of the likelihood to reach the target HR, was 4.66 for diltiazem vs. metoprolol. The mean HR for the metoprolol group did not reach the target of <100 bpm at any time during the 30-min study period Calculating for treatment effect size, Cohen's *d* was 1.31, which would be considered a large effect size.

2. How precise was the estimate of the treatment effect? (CI's?)	The estimate of treatment effect was not incredibly precise. 95% confidence interval was between 2.09 and 10.36, which is a rather large CI.
III **How can I apply the results to patient care?**	
1. Were the study patients similar to my patient?	Probably not. Authors exclude race which in this study population was likely skewed to Caucasian as Maimonides is located in the largest eastern European Ashkenazi demographic outside of Israel. African-American patients were likely under-represented. From an age perspective, the diltiazem group had an average age of 66.2 years, while the metoprolol group had a mean of 69.5 years. A 2012 AHA update lists the average age for men of 66.8 years and women of 74.6 years, which is similar to the study population. They did not report on all relevant comorbid conditions (HTN, CHF, Hx CAD, cardiomyopathy) that predispose to worse outcomes in AF patients. No reporting on whether patients were already on either agent. Roger, et al. Heart Disease and Stroke Statistics – 2012 Update. *Circulation*. 2012. 125(1): e2-e220.
2. Were all clinically important outcomes considered?	The only outcomes considered in this study was HR, as a measure of success of rate control and primary safety outcome measures that included HR < 60 bpm and SBP < 90 mm Hg. No other patient-centered outcomes (LOS, D/C from ED) were included.
3. Are the likely treatment benefits worth the potential harm and costs?	Possibly. Study is likely underpowered to identify harms. If reproducible, and in a patient population with new onset AF there appears to be a benefit in time to rate reduction. No economic analysis offered.

Limitations:
Convenience sample (M-F 8am-11pm) which predisposes to bias. Authors do not report on all potentially eligible patients that were not enrolled which in a 120,000 patient visit hospital is likely much higher than 52 patients.

Majority of patient were new onset AF suggesting less co-morbidities and healthier patients. Additional demographic data not provided making it difficult to generalize to broader populations

Potential unblinding at the data analysis level.

Dosing of metoprolol (max 10 mg) was less that typically used in the ED (5mg q 5 to 15mg) followed by an oral dose.

Clinical Bottom Line: In a select patient population with AF and RVR, diltiazem appears to be more effective than metoprolol at achieving rate control. Further RCT's are warranted in a broader patient population. The study is likely underpowered to have identified potential harms.