EVMS EM JC CRITICAL REVIEW FORM: THERAPY ARTICLES

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Citation: S.A. Alowais, B.D. Hayes BD, S.R. Wilcox, et al., Heart rate outcomes with concomitant parenteral calcium channel blockers and beta blockers in rapid atrial fibrillation or flutter. Am J Emerg Med 2020 May 8;735-757(20)

Study Objective: To determine the incidence of rate control achievement and bradycardia in patients in atrial fibrillation and flutter with RVR who receive concomitant intravenous beta-blocker and calcium channel-blocker.

Study Methodology:
Design: retrospective, single center, from April 2016-July 2018 (26 months).
Inclusion criteria: age >/= 18, initial HR >120, patient received an IV CCB and BB within four hours of each other (accounts for one half-life of overlap of most commonly used meds – diltiazem, verapamil, metoprolol).
Exclusion criteria: if second med was ordered but not given, if second med was initiated outside the ED, if post-administration heart rate was not recorded, if IV amiodarone or digoxin was administered.
Data regarding HR was obtained as averages at the following points of patient encounter: prior to administration of first agent, hourly prior to administration of second agent, and then 15 minutes, 30 minutes, 60 minutes, and 120 minutes after administration of second agent.
Target HR: <110.
Rebound HR: >110 within two hours of second agent.
Primary outcome: achievement of target HR within two hours of second agent.
Secondary outcome: bradycardia (HR <60) within two hours of second agent.
Statistical methods: descriptive statistics using Excel and SPSS for logic regression.

GUIDE	COMMENTS
I. Are the results valid?	
A. Did experimental and control groups begin the study with a similar prognosis?	Not really. Although there was no "control group" per se, baseline characteristics of patients were different. Almost half were already on B-blockers.
1. Were patients randomized?	N/A. Retrospective study
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?	N/A

3. Were patients analyzed in the groups to which they were randomized?	Yes
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	No reporting of prognostic factors such as history of CHF, MI, Cardiomyopathy, CKD, HTN, DM, Age >75 all associated with worse outcomes. No reporting of ICU vs. floor vs. D/C rates.
5. Were patients aware of group allocation?	Yes. There was no blinding of drugs given for rate control
6. Were clinicians aware of group allocation?	Yes. Drugs given were at the discretion of clinicians (selection bias)
7. Were outcome assessors aware of group allocation?	No mention that those collection data were blinded to the study hypothesis. This can be a means to address detection bias from those doing data analysis
8. Was follow-up complete?	Probably not. Authors report data collection for 120 minutes following last dose of second medication. Other than bradycardia there was no additional follow-up data reported.
What are the results ?	• 229 charts identified, 93 met exclusion criteria (mostly because the second agent was given late), 136 included • Mean age: 69.4y • 57.4% were male • Mean HR at presentation: 146.4bpm • 85.3% had Afib • Home meds: 47.8% on BB, 3.7% on CCB, 11.8% on both, 33.1% on nothing, <5pts on amiodarone or digoxin • First agent: 67.7% metoprolol • Mean time between last dose of first agent and administration of second agent: 88.4 minutes, though 56 patients received second agent within 60 minutes of the last dose of first agent • 52 patients were given IV magnesium • 46% met primary outcome of HR <110 within two hours of second agent • No association between age, initial HR, time between agents, or administration of IV mag and target HR achievement • Five patients developed bradycardia – four were asymptomatic (though one had a 15s sinus pause), one developed symptomatic

	bradycardia with vasopressors and ICU admission with hypotension developing after two measurement period • Of BP recordings, 8 of 89 patients developed hypotension (but no associated bradycardia) after second agent, no pts after first agent
1. How large was the treatment effect?	N/A
2. How precise was the estimate of the treatment effect? (CI's?)	N/A
III **How can I apply the results to patient care?**	At EVMS, we use diltiazem drips primarily. This study uses bolus dosing. (Do we?)
1. Were the study patients similar to my patient?	Hard to say. A majority of these patients likely had sig. comorbid conditions that was not described by authors. Half were on B-blockers. Unclear why almost 40% received Mg. Presumably based on age, gender and presenting HR were comparable.
2. Were all clinically important outcomes considered?	No. They considered target heart rate and incidence of bradycardia within two hours of the administration of a second agent. The half-life of diltiazem is ~3-4.5 hours and that of metoprolol is 3-4 hours (but may be 7-9 hours in poor metabolizers), therefore, two hours may be too short to evaluate for adverse effects. Additionally, there was no data reported about how many doses of the first medication were given or how far apart the doses of either medication were given. Therefore, we do not know if there was an adequate trial of the first medication. It may be the case that one medication would have worked if given more frequently or over a longer period of time. No patient centered outcomes such as hospital admission or LOS.
3. Are the likely treatment benefits worth the potential harm and costs?	Probably not. Authors do not provide sufficient data to assess harms. The study had a low rate of bradycardia, approximately 4%, with only one symptomatic bradycardia. However, this one patient had serious adverse effects as they were admitted to ICU with need for pressors. Additionally, it may be the case that more patients developed bradycardia after the two hour end-point used in the study.

Limitations:
Retrospective chart review with small N
Patient population and potential confounders were not clearly defined
Unclear what percentage were treatment naïve
No standardized approach to dosing
Unclear role for of use of Mg.?
No follow-up for additional harms.
Likely underpowered to report no statistical significance (Table 3) using a logistical regression model.

Clinical Bottom Line: The concomitant use dual agent therapy in those with AF who do not respond to initial therapy appears to provide no better odds than a coin flip (46%) regarding achieving adequate rate control and inconclusive data regarding potential harms.

Questions for discussion?

WHAT ARE THE PROS AND CONS OF DRIP VS PUSHES??

Though I could not find much data to answer this question, there was an interesting retrospective study from 2018 comparing Diltiazem infusion to oral immediate release for control of Afib. After receiving and IV bolus patients either were maintained on an infusion ro switched to oral immediate release Diltiazem. PO had tighter control at four hours: 73% PO vs 54% IV, with a treatment failure OR of 0.4 for PO compared to IV, which means that PO had a 2.6 OR for HR control. IV administration also resulted in a LOS two days longer than the PO group, which may be due to the time needed to transition to PO medications for outpatient use. The PO group was more likely to be admitted to the general medicine floor than stepdown. (Means KN, Gentry AE, Nguyen TT. Intravenous Continuous Infusion vs. Oral Immediate-release Diltiazem for Acute Heart Rate Control. *West J Emerg Med*. 2018;19(2):417-422. doi:10.5811/westjem.2017.10.33832)

HOW QUICKLY DO YOU WANT TO TREAT AFIB/FLUTTER??

It depends on the clinical scenario. If the patient is unstable (hypotension, myocardial ischemia, pulmonary edema, etc), rapid rate control with IV agents and/or immediate cardioversion. IV agents may be attempted first if patient is symptomatic but not unstable. If patient has mildly elevated HR (<120) or mild symptoms, oral agents may be attempted. (Uptodate - https://www.uptodate.com/contents/control-of-ventricular-rate-in-atrial-fibrillation-pharmacologic-therapy#H6)

WHAT IS THE FAILURE RATE OF DILTIAZEM DRIP FOR CONTROL OF AFIB/FLUTTER??

Derived from the Diltiazem AFib/Aflutter Study Group, Diltiazem is given with a first bolus of 0.25mg/kg over two minutes. If there is a 20% reduction in heart rate, an infusion is started at a rate of 5-15mg/h. If the first bolus does not work, a second bolus can be given at a dose of 0.35mg/kg. This strategy has a 94% success rate.
Metoprolol is dosed in boluses of 2.5-5.0 mg given over two minutes and repeated up to a total of 15mg.