Title: Oral vs Intravenous Diltiazem for Rapid Atrial Fibrillation/Flutter Trial (OVID RAF)

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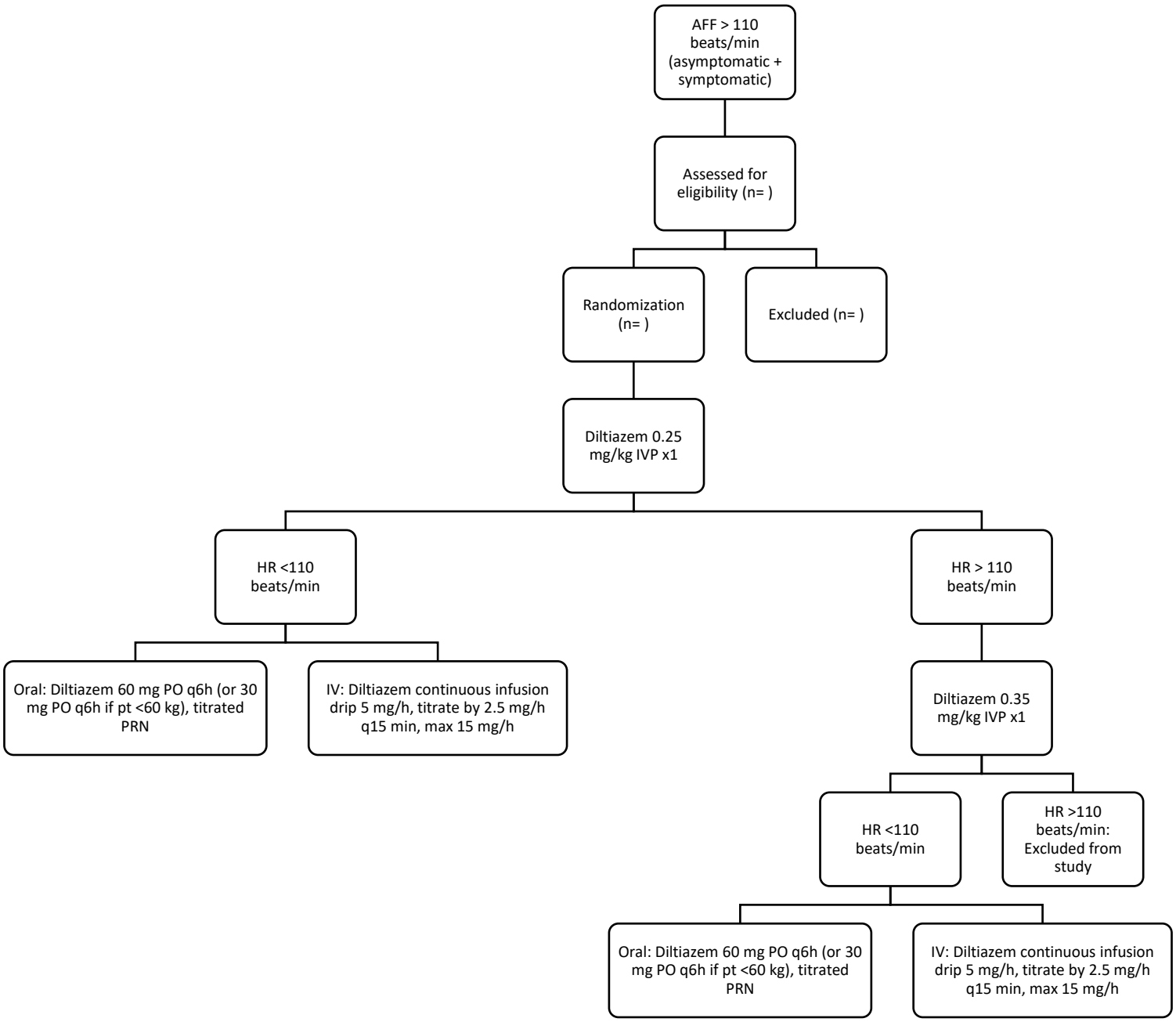
ORAL IMMEDIATE RELEASE VS. INTRAVENOUS CONTINUOUS INFUSION DILTIAZEM IN THE MANAGEMENT OF ATRIAL FIBRILLATION OR FLUTTER WITH RAPID VENTRICULAR RATE IN THE EMERGENCY DEPARTMENT: RANDOMIZED, CONTROLLED TRIAL

Study Protocol



Exclusion:

Unable to take PO, SBP <90 mmHg, HR <60 mmHg, WPW, history of allergy or idiosyncratic reaction to diltiazem

INTRODUCTION

Diltiazem, a non-dihydropyridine calcium channel blocker, is often the medication of choice in the rate control management of atrial fibrillation and flutter (AFF) due to its proven superiority over other rate control agents such as amiodarone, digoxin, and metoprolol.[i,ii,iii] It has a rapid onset of action, high response rate, and minimal negative inotropic effect. In the ED, a weight-based loading dose (LD) of IV diltiazem is usually administered followed by PO immediate release tablet or IV continuous infusion. Both options allow for dose titration in the short term before converting to the extended release PO formulation. The PO immediate release diltiazem tablet has a fast onset of action of 30-60 minutes and is dosed every 6 hours.[iv] Intravenous continuous infusion diltiazem has a variable onset of action with a titration frequency of every 15-30 minutes.

The route of diltiazem after the initial IV LD can potentially influence the disposition of the patient from the ED, the level of care needed, and hospital length of stay (LOS). However, no studies exist comparing PO immediate release and IV continuous infusion diltiazem. The objective of this study was to compare the incidence of patients who have a HR <110 beats/min or conversion to sinus rhythm at 2 hours after medication administration

METHODS

Study Design:

This was a prospective, open label, randomized non-inferiority trial to compare the effectiveness of PO immediate release diltiazem to IV continuous infusion diltiazem in achieving rate control in adult patients with atrial fibrillation or atrial flutter (AFF). This single center study was conducted at Virginia Commonwealth University Medical Center in Richmond, VA between 2018 and 2020. Approval of the

study was obtained from the hospital's institutional review board. All enrolled patients provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization documentation. This study is registered with clinicaltrials.gov, number _____.

Setting and Population:

The study was conducted in a tertiary medical center ED that treats over 95,000 patients annually. Patients were evaluated for enrollment if they were ≥ 18 years old, had a 12-lead electrocardiogram (ECG) showing AFF with a ventricular rate of >110 beats/min, and systolic blood pressure (SBP) of ≥ 90 mmHg. Patients were excluded if they were < 18 years old, pregnant, a prisoner, history of Wolff-Parkinson-White syndrome, received electrical therapy for cardioversion, or received other medications for acute HR control (besides adenosine) randomization, or had a history of allergic reaction to diltiazem.

Interventions:

Eligible patients gave written informed consent before entry into the study and the following data was obtained: demographics, medical history, vital signs, ECG findings. At the discretion of the health care provider, IV adenosine was administered to facilitate identification of the underlying arrhythmia.

Upon enrollment, patients received a diltiazem bolus of 0.25 mg/kg over 2 minutes. If the patient's HR did not decrease to <110 beats/min or decrease by 20% from baseline ventricular rate with the first diltiazem bolus within 15 minutes, but was well tolerated, patients were given a second bolus of 0.35 mg/kg IVP over 2 minutes. If the patient's HR did not decrease to <110 beats/min or decrease by 20% from baseline ventricular rate with the second diltiazem bolus they were excluded. Responders to the diltiazem bolus were then randomized in a 1:1 ratio, to receive diltiazem 60 mg PO immediate release (or 30 mg PO immediate release if patient was <60 kg) or be started on a diltiazem drip at 5 mg/h to be titrated by the nurse 2.5 mg/h every 15 minutes to a maximum of 15 mg/hr or until a HR of <110 beats/min or

conversion to normal sinus rhythm (NSR) occurred. Randomization was performed using block randomization.

Study data were collected and managed using REDCap electronic data capture tools hosted at Virginia Commonwealth Univeristy.[5] Baseline demographic information recorded included the patient's age, sex, race, vital signs (HR, BP, RR, oxygen saturation and oxygen requirement), weight, history of AFF, hypertension (HTN), congestive heart failure (CHF), and prior medication therapy (calcium channel blockers, beta-blockers, digoxin, other anti-arrhythmics). Diltiazem characteristics included initial IV diltiazem LD; maintenance oral and continuous infusion doses at 60 minutes, 2 hours, and 4 hours; and the use of adjunctive therapy for HR control at 4 hours was also collected. Clinical outcomes collected include HR and blood pressure (BP) at baseline, 60 minutes, 2 hours, and 4 hours; ED disposition; and hospital LOS.

Outcome Measures:

The primary efficacy outcome measures the incidence of patients who have a HR <110 beats/min or conversion to sinus rhythm at 2 hours after medication administration. Two hours was selected to give time for the PO IR diltiazem to have an effect, time for the diltiazem drip to be titrated and the ED physician to decide on disposition. Failure was defined as either a switch in therapy from PO immediate release diltiazem to IV continuous infusion diltiazem (or vice versa), the addition or switch of therapy to other rate control or antiarrhythmic agents within 2 hours, or a HR of > 110 beats/min at 2 hours.

Secondary outcomes included rate of conversion to sinus rhythm and identifying patient characteristics associated with HR control at 2 hours such as route of administration, age, weight, race, sex, initial heart rate and BP, and initial diltiazem LD. Safety outcome measures were HR <60 beats/min and SBP <90 mmHg for 15 minutes.

Statistical Methods:

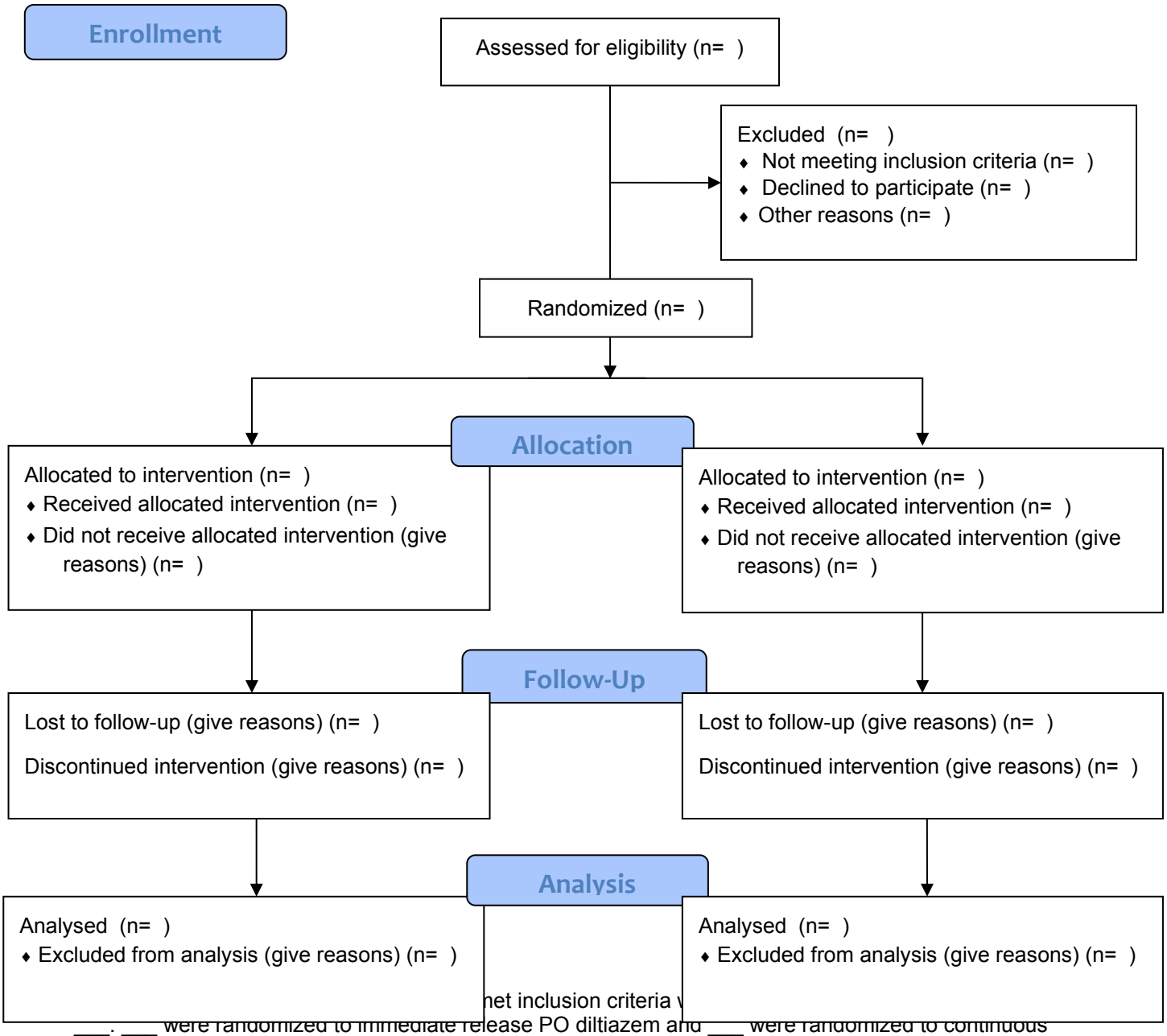
Analysis of efficacy used the intent to treat principle that included all randomized patients. The null hypothesis is that there is no difference in the achievement of HR <110 beats/min, decrease in ventricular rate by at least 20%, or conversion to sinus rhythm between the PO and IV diltiazem group at 2 hours.

Power calculation: A "Sealed Envelope Ltd" program was used to calculate sample size. The standard deviations used to calculate the sample size were based on an internal retrospective study that looked at immediate release PO vs. continuous infusion diltiazem for HR control in patients with atrial fibrillation. An estimate of 92 patients assigned in a 1:1 ratio to receive immediate release PO and continuous infusion IV diltiazem would achieve 90% power to detect non-inferiority using a one-sided, two-sample t-test. Margin of equivalence 10%.

Data were analyzed using Excel, R 3.2.2, and JMP 11.0.0 (Copyright 2013 SAS Institute, Cary, NC). Nominal variables were evaluated with X^2 and continuous variables were compared using the Student's t-test. Logistical regression modeling was used to identify patient characteristics associated with HR control at 2 hours. An a priori α level of ≤ 0.05 was used to determine statistical significance.

RESULTS

Figure 1: Flow Diagram



net inclusion criteria v
___. ___ were randomized to immediate release PO diltiazem and ___ were randomized to continuous infusion IV diltiazem. ___ patients were excluded for ___. Patient recruitment and randomization assignment for the trial are shown in Figure 1.

Table 1: Baseline demographics

Variable	Overall Summary N= (SD)	PO Group N= (SD)	IV Group N= (SD)	P-value (for t-test or X^2)
Age, y, (mean)				
Sex (Male)				
Race (Caucasian)				
Weight (kg)				
History of atrial fibrillation/flutter				
History of atrial flutter				
History of HTN				
History of CHF				
Prior medication therapy CCB BB Digoxin Antiarrhythmics				
Mean HR (beats/min)				
Mean SBP (mmHg)				
Mean DBP (mmHg)				
Atrial fibrillation on ECG				
Atrial flutter on ECG				
Duration of AFF episode <48 hours >48 hours unknown				
Received adenosine				
Mean initial diltiazem dose (mg/kg)				

Table 2: Characteristics associated with the primary endpoint

Variable	Difference	Unadjusted Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value
Age, y, (mean)					
Sex (Male)					
Race (Caucasian)					

Weight (kg)					
History of atrial fibrillation					
History of atrial flutter					
History of HTN					
History of CHF					
Prior medication therapy CCB BB Digoxin Antiarrhythmics					
Mean initial HR (beats/min)					
Atrial fibrillation on ECG					
Atrial flutter on ECG					
Duration of AFF episode <48 hours >48 hours UNKNOWN					
Mean initial diltiazem dose (mg/kg)					

PO: Oral
IV: Intravenous
LD: Loading dose
HR: Heart rate
kg: Kilogram
mg: Milligram
CI: Confidence interval

Table 3: Conversion to sinus rhythm

Time	**PO (%)**	**IV (%)**	**P-value**
After bolus			
60 minutes			
2 hours			
4 hours			

Table 4: ED Disposition

ED Disposition	**PO Group**	**IV Group**
Discharge		
General floor with telemetry		
Stepdown		

ICU		
Hospital LOS		

PO: Oral
IV: Intravenous

[i] Schreck DM, Rivera AR, Tricarico VJ. Emergency management of atrial fibrillation and flutter: intravenous diltiazem versus intravenous digoxin. *Ann Emerg Med*. 2016;29(1):135-140.
[ii] Siu C, Lau C, Lee W, Lam F, Tse H. Intravenous diltiazem is superior to intravenous amiodarone or digoxing for achiving ventricular rate control in pateints with acute uncomplicated atrial fibrillation. *Crit Care Med*. 2009;37:2174-79.
[iii] Fromm C, Suau SJ, Cohen V, Likourezos A, Jellinek-Cohen S, Rose J, Marshall J. Diltiazem vs. metoprolol in the management of atrial fibrillation or flutter with rapid ventricular rate in the emergency department. *J Emerg Med*. 2015;49(2):175-82.
[iv] Lexicomp Online®, Lexi-Drugs® Hudson, Ohio: Lexi-Comp, Inc.; June 29, 2016.