Official Title: Diltiazem in the Treatment of Atrial Fibrillation or Atrial Flutter With Rapid Ventricular Rate (AFF RVR): Comparing Calcium Pre-treatment vs Placebo in Prevention of Diltiazem Induced Hypotension

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PROTOCOL TITLE

Diltiazem in the treatment of atrial fibrillation or atrial flutter with rapid ventricular rate (AFF RVR): Comparing calcium pre-treatment vs placebo in prevention of diltiazem induced hypotension

- **SPONSOR**

N/A

- **PROTOCOL Version Number and Date:**

Version 2. June 22nd, 2023

- **PRINCIPAL INVESTIGATOR**

Michael Cirone, MD

- **STUDY SUMMARY**

Non-dihydropyridine calcium channel blockers (CCB) are routinely used in the treatment of atrial fibrillation or flutter with rapid ventricular response (AFF with RVR) however, their use can be limited by drug induced hypotension. This drug induced hypotension limits and complicates CCB use in the treatment of AFF with RVR. Calcium pre-treatment with calcium channel blocker administration has been studied extensively with verapamil administration in preventing drug induced hypotension however, similar studies evaluating calcium pretreatment with diltiazem administration in the prevention of drug induced hypotension are limited.

The purpose of our study is to compare the relative efficacy and safety for calcium pretreatment with diltiazem in the treatment of AFF with RVR in preventing drug induced hypotension. This prospective, randomized double-blinded study will evaluate patients who present to the emergency department at Advocate Christ Medical Center (ACMC) with a diagnosis of AFF RVR with ventricular rate greater than or equal to 120 bpm from IRB approval to June 1, 2024. Via simple randomization, patients will be administered Calcium pre-treatment vs control prior to diltiazem administration. Calcium gluconate 1gm or 100 mL of normal saline will be administered as an intravenous infusion over 5 minutes followed by bolus diltiazem 0.25 mg/kg IV push (with a 20mg max) with repeat diltiazem bolus dose after 15 minutes if rate control not achieved 0.35mg/kg IV push. Calcium gluconate will not be administered with repeat doses of diltiazem. Weight-based dosing of diltiazem was most utilized, though some

providers may elect to modify based on the clinical scenario. The primary outcome will be the mean difference in systolic blood pressure (SBP) evaluated at 5 and 15 minutes after administration of diltiazem bolus. Secondary outcomes include decrease in heart rate, conversion to sinus rhythm, and adverse effects of medication administered.

- **OBJECTIVES**

To compare the relative efficacy for calcium pre-treatment in decreasing incidence of drug induced hypotension after diltiazem administration for treatment of AFF with RVR.
Null Hypothesis: There will be no difference between groups in incidence of hypotension after pretreatment with calcium prior to bolus of diltiazem.

- **BACKGROUND/LITERATURE REVIEW**

Atrial fibrillation accounts for more than 454,000 hospitalizations each year in the United States.[1] Rapid ventricular response (RVR) is a potential sequelae of atrial fibrillation which results in loss of atrial kick, shortened ventricular filling, increased myocardial oxygen demand and ultimately hemodynamic instability.[2] Treatment guidelines from the American Heart Association recommend intravenous beta blockers, non-dihydropyridine calcium channel blockers, or Amiodarone/Digoxin in the treatment of atrial fibrillation with RVR.[3] Diltiazem is one of the most commonly used CCB to treat AFF with RVR.[4]
Despite AFF with RVR being a common disorder and commonly treated with diltiazem, there are known limitations and complications of drug induced hypotension. Nationally, and within the ACMC ED, there is no consensus to the management of atrial fibrillation with rapid ventricular response. Management options include calcium channel blockers (predominantly diltiazem), beta blockers (predominantly metoprolol), and antiarrhythmics like amiodarone and digoxin. When employing calcium channel blockers standard of care includes the possibility of calcium pretreatment in an effort to prevent drug induced hypotension. Several studies have shown that verapamil with calcium pretreatment results in decreased incidence of drug induced hypotension; however, studies analyzing pretreatment of calcium with diltiazem in decreasing drug induced hypotension are limited .[5,6] In recent years, physician preference and comfort has led to increased utilization of diltiazem (rather than verapamil) in managing atrial fibrillation with RVR. As a result, evidence of calcium's efficacy in conjunction with this specific nonDHP is lacking.

Diltiazem has a mechanism which inhibits the flow of calcium into the myocardium and is widely used in the treatment of AFF with RVR. It has also been utilized in the treatment of paroxysmal supraventricular as its mechanism causes slowing of AV nodal conduction time and prolongs the AV nodal refractory period.[7] Furthermore, diltiazem inhibits the inflow of calcium ions on vascular smooth muscle, causing vasodilation and ultimately decreasing peripheral vascular resistance. This, in combination with its negative inotropic effects, results in a decrease in blood pressure, which is frequently seen with its administration. Prior studies including in vitro and animal data suggest that pretreatment with calcium prior to CCB administration may minimize the effects on cardiac output and blood pressure.[8] In the setting of AFF with RVR, these effects of decreased blood pressure and cardiac output can limit the safety of CCB use. This study aims to evaluate the impact of calcium pretreatment in decreasing the incidence of drug induced hypotension.

- **SUMMARY OF METHODS**
  - **Study Design**

Single center, prospective, double-blinded (prescriber and patient), randomized-controlled trial

- **Setting**

Advocate Christ Medical Center Emergency Department (ACMC ED)

- **Population**

Patients presenting to ACMC ED with a primary diagnosis of AFF with RVR from IRB approval to June, 2024

- **Sample Size**

• A maximum of 92 subjects (46 subjects treated with Calcium and 46 subjects treated with control) will be included in this prospective randomized study based on estimates of patients presenting to the Emergency Department with a primary diagnosis of AFF RVR. With this sample size, we will have 80% power to detect a mean difference of 10.5 mmHg between groups for the primary outcome of mean Numeric Rating Scale with an alpha of 0.05, anticipating a 25% dropout rate (at most).

- **Recruitment**

Patients presenting to Advocate Christ Medical Center emergency department with a diagnosis of AFF with RVR from IRB approval to (to be determined) seven days a week while a pharmacist is present. The ED physician or ED PharmD providing care for the patient will identify patients' eligible for the study and one of the ED PharmDs listed on the personnel delegation log will consent the patient. The pharmacist will document consent in the EMR using an EPIC smartphrase.

- **Inclusion criteria**[7]

- Age ≥ 18 years or older
- Able to provide informed consent
- Primary diagnosis AFF with RVR greater than or equal to 120 bpm

- **Exclusion criteria**[7]

- Pregnancy defined as a positive urine HCG
- Hemodynamically unstable patients (SBP <90, MAP <65)
- Stated history of systolic heart failure with reduced ejection fraction (<40%) or evidence of acute heart failure or reduced EF (peripheral edema, JVD, pulmonary edema) on clinical exam or bedside echo
- Patients with left ventricular assist device
- Sinus node dysfunction or preexcitation with accessory pathway (known diagnosis of SVT, WPW or sick sinus syndrome. Delta waves or other evidence of accessory pathway on EKG)
- 2nd or 3rd degree atrioventricular block
- Allergy or sensitivity to any study drugs
- Previously enrolled in this trial during a different patient encounter
- Non-English speaking

- **Vulnerable Populations**

N/A

- **Study Endpoints**

Primary Endpoints:[7]

- Mean difference in SBP evaluated at 5 and 15 minutes after initiation of infusion of diltiazem

Secondary Endpoints:[7]

- Change in heart rhythm at 5 and 15 minutes after initiation of infusion of diltiazem
- Mean change heart rate at 5 and 15 minutes after initiation of infusion of diltiazem
- Adverse effects due to administration of medications
- Clinical need for rescue medication administration

- **Measures/Instrumentation**

Blood pressure at baseline 5 and 15 minutes after administration of Diltiazem infusion

- **Study Procedures**

Patients presenting to Advocate Christ Medical Center emergency department (ED) with a diagnosis of AFF with RVR from IRB approval to June 1, 2024 twenty four hours a day, seven days a week. The ED physician will identify patients eligible for the study and alert the ED pharmacist who will consent the patient using the consent form (attached). An EPIC dot.phrase will utilized to capture informed consent for this study (example below). Each patient will be handed a copy of the consent form and signed consent forms will be kept at Advocate Christ Medical Center in the PI's locked office. This study will be registered at clinicaltrials.gov by Dr Cirone.

Example/tentative dot.phrase for document informed consent for this study:

.calciumpretreatmentvsplaceboprevention diltiazeminducedhypo
RESEARCH PROGRESS NOTE
Study Title:
IRB #:
Brief Description:
PI: Dr. Cirone

Via simple randomization, patients will be allocated to one of two study drug groups, either the intervention (calcium gluconate) or control (normal saline) group. Once the order for the study drug is put in by the ED physician or ED pharmacist and verified, the ED pharmacist will retrieve the study drug from the medicine automated dispensing cabinet (Pyxis) located in the ER. The study drug and the placebo will be stored in pyxis in a kit format which will include diluent (NS) and the study drug or placebo (NS) vials. These kits will be created by a pharmacist or technician not participating in the study according to a randomization schedule on a password encrypted excel sheet in the pharmacy G drive. This will only be accessible by the pharmacist creating these study kits. All the vials in the study kit will be covered to keep the drugs blinded to both investigators and the patients. The ED pharmacist will deliver the study drug to the bedside nurse for administration. The pharmacists, physicians, and nurses participating in administration of the medications will be blinded to which drug is being administered. Inclusion in the study will not result in any additional cost to the patient.

Medication administration:
Study drug (Calcium gluconate 1 gram/100ml 0.9% NaCl or 100ml 0.9% NaCl)over 5 minutes). Immediately after administration of the study drug, diltiazem will be administered as an IV push over 5 minutes. Additional doses of diltiazem

IV push over 5 minutes are permissible, however no additional doses of study drug will be administered.

The primary outcome of this study will be the Mean difference in SBP evaluated at 5 and 15 minutes after administration of diltiazem bolus. Monitors were set to obtain an automated full set of vitals every 5 minutes after administration of diltiazem. Secondary endpoints include mean change heart rhythm at 5 and 15 minutes after administration of diltiazem bolus, mean change heart rate at 5 and 15 minutes after administration of diltiazem bolus, adverse effects due to administration of Calcium gluconate and adverse effects due to administration of Diltiazem infusion.
Adverse events will be assessed by the ED pharmacist at the specified time intervals including but not limited to nausea, vomiting, lightheadedness, headache or extravasation.
The following data points will be collected: medical record number (MRN), age, gender, race, weight, height, initial vitals (heart rate, blood pressure, respiratory rate, temperature, and oxygen saturation), repeated vitals, past medical history, medications taken prior to arrival, hospital length of stay and medications given for treatment failure along with their routes and dosages.

Confidentiality will be maintained to the extent possible. Furthermore, information will be kept on a password protected computer located at Advocate Christ Medical Center in the PI's locked office. The recorded data will be destroyed following completion of study, analysis of data and dissemination of our findings.

Monitoring Plan:

INTRODUCTION
The monitoring plan includes reviews for both data integrity and minimization of risk to patients involved in the study. The principal investigators Dr. Cirone, co-investigators, research biostatistician Cindy Ndiaye, and the Advocate Aurora Health Care Institutional Review Board will be involved in the interim monitoring activities. Monitoring will be conducted in accordance with applicable regulations and institutional/IRB policies.

PURPOSE
The purposes of controlled trial quality monitoring reviews are to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

(c) The conduct of the trial follows the currently approved protocol/amendment(s) and applicable regulatory requirement(s).

ROLES/REVIEWS

Principal investigators and co-investigators: The principal investigators, co-investigators, and research biostatistician will carefully assess and evaluate the first nine subjects enrolled in controlled trial to monitor for any rare adverse outcomes that may or may not have been known prior to study start. The same assessment will be performed at the midpoint of the study, after the 46th subject is enrolled. A stopping plan, explained further under the over-view, will be enacted at the midpoint interim look.

For all subjects, the Principal Investigators and co-investigators will continue to review all adverse outcomes and will regularly monitor the data to identify trends throughout the study. The Principal Investigator and co-investigators will be responsible for reporting all adverse events to the IRB and for revising the protocol as needed to maintain safety. Primarily, the Principal Investigators, co-investigators, and research biostatistician will be responsible for the IRB submissions, ClinicalTrials.gov registration, safety reporting and other regulatory components of the study.

QUALITY MONITORING REPORT OVER-VIEW

The primary and co-investigators will conduct a monitoring report with the research biostatistician to occur prior to enrollment of the 10^{th} subject and again at the midpoint of the study after the enrollment of the 46th subject for a total of two interim looks. The quality monitoring review must include an assessment of the following records and results must be submitted to Advocate Aurora Health Institutional Review Board:

1) Regulatory and IRB files (e.g., protocol, consent form, study team CITI training and curriculum vitae, delegation of authority log, IRB approvals and correspondence).
2) Subject chart review for all subjects consented/enrolled, assessing for appropriately obtained consent, accuracy of eligibility, and all follow-up data collected.
3) Any adverse events reported thus far.
4) Drug accountability and storage.

A stopping plan will also be put in motion to minimize risk of Type I error. The plan consists of using the O'Brien-Fleming boundary to test at the second interim look (n=46) if the probability of the randomized-control trial rejecting a false null hypothesis is <0.05. If the probability is >0.05, then the experiment will be stopped.

- **DATA MANAGEMENT PLAN**

The following study variables will be collected based on the study objectives:

- Medical Record Number (MRN)
- Age
- Gender
- Race
- Ethnicity
- Weight
- Height
- Initial vitals (heart rate, heart rhythm, blood pressure, respiratory rate, temperature and oxygen saturation)
- Past Medical History
- Serum Calcium if available prior to medication administration (as measured on complete metabolic panel)
- Hospital length of stay
- Medications given for treatment failure
- Dose and route of rescue medications given
- Time to administration of medication
- Repeat Vitals following medication administration (heart rate, heart rhyhtm, blood pressure, respiratory rate, temperature and oxygen saturation)

All data will be collected, and confidentiality will be maintained. Furthermore, information will be kept on a password protected computer located at Advocate Christ Medical Center in the ED administration office. The recorded data will be destroyed following completion of study and analysis of data. Data collection and analysis will only be conducted by the members of the research team. If data is needed to transported, it will only be done by the research team and will only be transported between team members. Transfer of data will be done person to person or electronically via a password protected drive.

All information gathered during this study will be kept confidential. Study data will be managed using REDCap[16] electronic data capture tools hosted by Advocate Health Care. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The

data will be accessible to only the study investigators and REDCap administrators. Subjects will be assigned case numbers. Data being extracted from the REDCap database will include only the case numbers and be de-identified via the electronic removal of PHI prior to data download. After data collection is complete and records have been verified, identifiers will be permanently removed from the data set. Any study documentation including regulatory information, consent forms, and data collection forms will be secured in a locked cabinet in the pharmacy resident's locked office and ill be destroyed upon completion of the study and analysis of the data.

- **Data Analyses**

A maximum of 92 subjects (46 subjects treated with Calcium and 46 subjects treated with control) will be included in this prospective randomized study based on estimates of patients presenting to the Emergency Department with a primary diagnosis of AFF RVR. With this sample size, we will have 80% power to detect a mean difference of 10.5 mmHg between groups for the primary outcome of mean Numeric Rating Scale with an alpha of 0.05, anticipating a 25% dropout rate (at most).

Descriptive statistics will be calculated for all variables and presented overall and by group using mean ± SD for continuous variables and count/percentages for categorical variables. Comparisons will be made between groups for all outcomes using Chi-Square or Fisher's exact tests as necessary for categorical data and a one-way ANOVA as appropriate for all continuous data. All tests will be two-tailed and a p-value of 0.05 will be considered statistically significant in all analyses. We will also assess utilizing multiple predictive multivariate logistic regression models.

- **BENEFITS**

There will be no direct benefit for participating in this study.

- **RISKS**

Common adverse effects associated with standard of care medications. [10-11]

- Calcium: hypotension, bradycardia, tingling, upset stomach
- Diltiazem: lightheadedness, weakness, nausea, headache

- **AVAILABLE RESOURCES**

Advocate Christ Medical Center has a rich history of conducting clinical research by qualified and experienced investigators. Multiple resources will be available throughout the study. Members of the research team have extensive experience in conducting research and in their designated areas of practice. The research team is committed to the study and will be available to be reached at any time for questions or any problems that may arise.

Michael Cirone, M.D. – Emergency Medicine Physician
Marc McDowell, Pharm.D. – ED Clinical Pharmacist
Cindy Ndiaye, MPH – Research Coordinator
Nadine Lomotan, Pharm.D. – ED Clinical Pharmacist
Barb Bukowski, Pharm.D. – ED Clinical Pharmacist
Kara Fifer, Pharm.D. – ED Clinical Pharmacist
Kate Roels, Pharm.D. – ED Clinical Pharmacist
Andrew McInerney, Pharm.D – Emergency Medicine Pharmacy Resident
Siri Krishna Khalsa, M.D. – Emergency Medicine Resident
Connor Corrente, M.D. – Emergency Medicine Resident

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- **ABBREVIATIONS & ACRONYMS**

AFF with RVR - Atrial fibrillation or flutter with rapid ventricular response
ANOVA – Analysis of Variance
CCB – Calcium channel blocker
ED – Emergency Department

- **DATA DICTIONARY**

  - Medical Record Number (MRN)
  - Age
  - Gender
  - Race
  - Weight
  - Height
  - Initial vitals (heart rate, blood pressure, respiratory rate, temperature and oxygen saturation)
  - Past Medical History
  - Hospital length of stay
  - Medications given for treatment failure
  - Dose and route of rescue medications given
- Time to administration of medication