Document Coversheet

Study Title: Repeated Amiodarone Dosing In Cardiac surgicaL Procedures

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COMPARING THE EFFECTIVENESS OF TWO DIFFERENT AMIODARONE DOSING STRATEGIES TO TREAT STABLE ATRIAL FIBRILLATION AFTER NON-EMERGENT CARDIAC SURGERY

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ABBREVIATIONS

AE	Adverse event
AF	Atrial fibrillation
BPM	Beats per minute
CABG	Coronary artery bypass graft
CDR	Conventional dosing regimen
HR	Heart rate
HIPAA	Health insurance portability and accountability act
ICF	Informed consent form
ICU	Intensive care unit
IRB	Institutional review board
IV	Intravenous
LAR	Legally-authorized representative
NSR	Normal sinus rhythm
ORI	Office of research integrity
PI	Principal Investigator
RBDR	Repeated bolus dosing regimen
RVR	Rapid ventricular response
SAE	Serious adverse event
SBP	Systolic blood pressure
SID	Subject identification number
UBACC	University of San Diego Brief Assessment of Capacity to Consent
UKCMC	University of Kentucky Chandler Medical Center

1. BACKGROUND

Atrial fibrillation (AF) is a common complication following cardiac surgery, occurring in approximately 33% of all patients after cardiac surgery. AF can sometimes cause a rapid ventricular rate (RVR), defined as a HR greater than 110 beats per minute (BPM). AF is typically characterized as either stable (systolic blood pressure (SBP) ≥ 90 mmHg) or unstable (SBP <90 mmHg). Patients with unstable AF with or without RVR may require immediate electrical cardioversion to restore normal sinus rhythm (NSR) and an appropriate blood pressure; whereas, patients with stable AF frequently undergo medical therapy to either treat RVR or to restore NSR.

Amiodarone is a class III antiarrhythmic with beta-blocker activity that also blocks myocardial potassium, sodium and calcium channels. In stable AF, amiodarone is frequently given to control the HR and restore NSR after cardiac surgery. In this setting, amiodarone is commonly given as an initial intravenous (IV) bolus (150 mg IV) followed by a combined IV and oral load to a total dose of 8 gm. Because of amiodarone's beta-blocker activity, the IV bolus is associated with a reduced HR and may lead to restoration of NSR on its own. For this reason, some clinicians will provide up to 5 additional IV amiodarone boluses during the drug's loading period to treat RVR. Other clinicians will not specifically treat RVR in stable AF and will continue with the routine amiodarone IV and oral load. At this time, both dosing regimens are routinely used for patients after cardiac surgery, the decision to use one over the other is made based on clinician preference. It is not known whether the repeated amiodarone dosing regimen is better than the conventional amiodarone dosing regimen with regard to successful conversion to NSR or the time to conversion to NSR in patients with stable AF.

2. STUDY HYPOTHESIS

We hypothesize that, compared to a conventional dosing regimen (CDR), a repeated bolus dosing regimen (RBDR) of amiodarone will result in an increased percentage of patients who convert to normal sinus rhythm within 24 hours of initial AF.

3. OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to compare, in patients who develop stable AF after non-emergent cardiac surgery, the percentage of patients who have converted to NSR at 24-hours after receiving a repeated amiodarone bolus and loading dose regimen to the percentage of patients who have converted to NSR after a conventional amiodarone IV loading dose regimen.

3.2 Secondary Objectives

The secondary objectives of this study are:

- Compare the total time, in minutes, during the first 24 hours that the patient achieves target HR (HR < 110 bpm) between patients who receive a repeated amiodarone bolus dosing regimen and those who receive a conventional amiodarone bolus dosing regimen.
- Compare the time to achieve target HR (HR < 110 bpm) between patients who receive a repeated amiodarone bolus dosing regimen and those who receive a conventional amiodarone bolus dosing regimen.

- Compare the time to achieve NSR between patients who receive a repeated amiodarone bolus dosing regimen and those who receive a conventional amiodarone bolus dosing regimen.
- Compare the percentage of patients who achieve NSR by ICU discharge and hospital discharge between patients who receive a repeated amiodarone bolus dosing regimen and those who receive a conventional amiodarone bolus dosing regimen.
- Compare the percentage of patients who have recurrent AF before ICU discharge and before hospital discharge between who patients who receive a repeated amiodarone bolus dosing regimen and those who receive a conventional amiodarone bolus dosing regimen.
- Compare the incidence and severity of hypotension between patients who receive a repeated amiodarone bolus dosing regimen and those who receive a conventional amiodarone bolus dosing regimen.
- Compare the incidence and severity of conduction abnormalities between patients who receive a repeated amiodarone bolus dosing regimen and in those who receive a conventional amiodarone bolus dosing regimen.
- Compare the incidence and severity of amiodarone-related pulmonary fibrosis between patients who receive a repeated amiodarone bolus dosing regimen and those who receive a conventional amiodarone bolus dosing regimen.

3.3 Exploratory Objectives

The exploratory objectives of this study are:

- Evaluate preoperative, intraoperative and postoperative factors that affect the efficacy of the amiodarone dosing strategy in achieving NSR at 24 hours, ICU discharge and hospital discharge.
- Evaluate preoperative, intraoperative and postoperative factors that affects the safety profile of the repeated amiodarone bolus dosing regimen.

4. STUDY DESIGN

This study is a single-center, prospective, randomized, open-label trial of subjects who develop AF after non-emergent cardiac surgery at the University of Kentucky Chandler Medical Center (UKCMC). Patients will be randomized to receive either a conventional amiodarone dosing regimen (CDR) or to a repeated amiodarone bolus dosing regimen (RBDR).

5. STUDY POPULATION

This study will include 150 patients undergoing non-emergent cardiac surgery. We anticipate approximately 60 of these patients will develop stable AF in the postoperative period. Patients will be ≥ 18 years of age. The proposed dates of enrollment will be July 1, 2021 through June 30, 2023 or until full recruitment has been completed, whichever comes first.

5.1 Inclusion criteria

To be enrolled in this study, the subject must meet all of the following criteria:

- Subject must be ≥ 18 years old
- Subject must be willing to give written informed consent

- Subject must undergo non-emergent cardiac surgery, including coronary artery bypass grafting (CABG), non-infectious valve repair or replacement, atrial or septal defect repair, thoracic aortic replacement surgery or any combination of these procedures

5.2 Exclusion criteria

The subject will be excluded from the study if any of the following criteria are met:

- Documented allergy to amiodarone or iodine
- History of atrial fibrillation or other heart conduction system abnormality
- History of cardiac maze, pulmonary vein isolation, or other procedure affecting the conduction system
- Scheduled cardiac maze, pulmonary vein isolation, or other procedure affecting the conduction system
- Low cardiac index or cardiogenic shock requiring pharmacologic or mechanical support
- History of pre-existing respiratory system disease requiring oxygen therapy prior to admission
- History of cirrhosis or other chronic liver disease
- Pregnancy or breastfeeding mothers
- Prisoners

6. SUBJECT RECRUITMENT METHODS AND PRIVACY

Subjects will be screened and recruited in one of three ways.

First, potential subjects will be primarily screened in the Anesthesiology Preoperative Clinic and recruited by the PI or a member of the IRB-approved research team. These subjects will be consented for this study by the PI or a member of the IRB-approved research team during a scheduled clinic visit. The screening process will utilize ordinary standard of care procedures (e.g., medical evaluation, physical examination and diagnostic testing at the discretion of the attending cardiovascular surgeon and/or perioperative anesthesia team). Prior medical records documenting these evaluations, examinations and testing may be used as source documents for the baseline visit.

Second, because some patients may be hospitalized prior to their operation and will not present to the Anesthesiology Preoperative Clinic prior to their operation, hospitalized patients scheduled for surgery will be screened and consented using the above process prior to their operation.

Third, because some outpatients will not present to the Anesthesiology Preoperative Clinic and some inpatients will not be screened and consented prior to their operation, for a variety of reasons. These patients will be screened in the early postoperative period, after admission to the ICU. These patients will be recruited by the PI or a member of the IRB-approved research team. The screening process will utilize ordinary standard of care procedures (e.g., medical evaluation, physical examination and diagnostic testing at the discretion of the attending cardiovascular surgeon and/or perioperative anesthesia team). Prior medical records documenting these evaluations, examinations and testing may be used as source documents for the baseline visit.

Regardless of recruitment pathway, during the screening and recruitment process, the PI or another member of the research team will verify that the eligibility criteria have been met. Preoperative outpatients who meet the inclusion and exclusion criteria will be approached for informed consent. Inpatient preoperative and all postoperative patients who meet the inclusion and exclusion criteria will be further assessed for the continuous infusion of sedating agents. For these patients, the legally-authorized representative (LAR) will be approached for informed consent. For postoperative patients who meet the inclusion and exclusion criteria and are not receiving a continuous infusion of sedating agents, the University of San Diego Brief Assessment of Capacity to Consent (UBACC) test will be performed. For patients with a UBACC score of <18, the LAR will be approached for informed consent. For patients with a UBACC score of ≥ 18, informed consent will be discussed with the patient. Written informed consent and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained prior to performance of any protocol-specific procedures.

7. ADVERTISING

None.

8. INFORMED CONSENT PROCESS

A full consent discussion will be held with the patient or legally-authorized representative LAR at which time the study protocol, procedures, risks/benefits, alternatives, and the voluntary nature of the research will be explained by the study staff. There will be an opportunity for the patient or LAR to ask questions and for private consideration/discussion with family, if needed. If the patient or LAR wishes to be involved in the protocol, study procedures will begin after the

patient's or LAR's signature is obtained on the informed consent and HIPAA documents. If the patient would like to take time outside the clinic visit to decide about enrollment, the patient may return the signed consent to their next visit, including preoperatively on the day of surgery. For patients who have LAR consent and are no longer on continuous infusions of sedation and who regain consciousness and their UBACC score improves to ≥ 18, the patient themselves will be re-consented using the process and procedures previously described. No study procedures will begin until after the signed copy of the informed consent and HIPAA documents are obtained. A note in the patient file will be written explaining how the patient meets study criteria, the process of informed consent and the nature of the discussion, and who participated in the consent process. This note will be generated by the PI or another member of the study team.

9. RESEARCH PROCEDURES

All enrolled patients will receive the standard of care perioperative institutional protocol for their cardiac surgical procedure. The preoperative and intraoperative management will be performed at the discretion of the cardiovascular surgery team, the anesthesia team, and other healthcare teams. The postoperative management will be performed at the discretion of the cardiovascular surgery team and the consultant anesthesiology critical care team according to standard management protocols.

As part of standard postoperative management, all patients will undergo continuous electrocardiographic (ECG) monitoring in the postoperative period. If new AF is identified within the first 72 hours after they are admitted to ICU following their surgical procedure, the patient will be assessed for hemodynamic stability. If the patient is unstable (SBP <90 mmHg)

or requires a significant increase in vasopressor infusion (an increase of more than 1.5x in baseline infusion rate) to maintain SBP>90 mmHg, the standard of care patient management will be provided and the patient will not be randomized to either study group. If the patient is stable (SBP>90 mmHg and requires less than 1.5x more vasopressor infusion to maintain SBP>90 mmHg), the patient will be given up to 15 mg IV metoprolol, in divided doses, and monitored for 20 minutes for conversion to NSR. If stable AF persists, the patient will be randomized according to the plan described below to either the conventional amiodarone dosing regimen (CDR) or to the repeated amiodarone bolus dosing regimen (RBDR).

Patients in both groups will receive an amiodarone bolus of 150 mg IV over 10 minutes then a 24-hour amiodarone loading infusion (1 mg/min for 6 hours followed by 0.5 mg/min for 18 hours). After these infusions have been completed, patients in both groups will receive additional enteral (400 mg amiodarone oral or per tube three times daily or 2 times daily if the patient has gastrointestinal intolerance when taking the drug three times daily) or intravenous amiodarone (0.5 mg/min continuous infusion) to complete an 8-gm total amiodarone load. After the amiodarone load is completed, patients in both groups will receive maintenance amiodarone (200 mg amiodarone oral or per tube once daily). Further management of amiodarone dosing will be at the discretion of the attending cardiac surgeon, critical care medicine specialist or cardiologist. Other medications will be at the discretion of the attending cardiac surgeon, critical care medicine specialist or cardiologist. Patients will be monitored continuously throughout the 24-hour amiodarone IV load time period according to standard protocol.

9.1 Conventional Dosing Regimen (CDR)

Patients randomized to the CDR group will receive the previously-described amiodarone bolus followed by a 1.0 mg/min IV amiodarone infusion for 6 hours and then a 0.5 mg/min IV amiodarone infusion for 18 hours.

9.2 Repeated Bolus Dosing Regimen (RBDR)

Patients randomized to the RBDR group will receive the previously-described amiodarone bolus followed by a 1.0 mg/min IV amiodarone infusion for 6 hours and then a 0.5 mg/min IV amiodarone infusion for 18 hours. In addition, patients in the RBDR will receive an additional 150 mg IV amiodarone bolus whenever the patient develops tachycardia (Heart Rate (HR) ≥ 110 beats per minute) lasting more than 10 minutes. This bolus may be repeated up to a total of 5 times (6 total boluses) over the first 24 hours.

9.3 Informed Consent

The PI or another study team member will explain the study to the subject, answer all of the subject's questions, and obtain written informed consent before the collection of any study data or performance of any study-related procedures.

The subject must be willing and able to sign and date the informed consent form (ICF) prior to the collection of any study-related data. The original, signed informed consent will be retained with the subjects' records and a copy provided to the subject.

9.4 Enrollment

All subjects who sign the ICF will be considered eligible for this study. Subjects who are eligible and meet all the inclusion criteria and do not meet any of the exclusion criteria will be considered enrolled in the study. Enrolled patients who have persistent, stable AF will be randomized and treated according to the research procedures described above.

9.5 Randomization

All enrolled patients who develop persistent, stable AF will be randomized using a simple randomization scheme.

9.6 Assignment of Subject Identification Number

All enrolled subjects will be assigned a three-digit subject identification number in sequential order, starting with 001.

10. DATA COLLECTION

Preoperative, intraoperative, and postoperative data will be recorded and entered in the appropriate data collection sheets for all randomized patients. Study data will not be collected on non-enrolled patients or enrolled patients who are not randomized. Data will include, but is not limited to, previously-obtained preoperative, intraoperative, and postoperative data, concomitant procedures, procedure related complications and adverse events. All study data will be maintained on a REDCap database and will only be accessed for study purposes. A list of the data to be collected is provided below:

10.1 Preoperative data

- Demographics (sex, age, height, weight, and body mass index)
- Preoperative use of beta-blocker therapy
- Preoperative left ventricular ejection fraction
- Preoperative tobacco use (smoking)
- Preoperative alcohol use
- Preoperative benzodiazepine use

10.2 Intraoperative data

- Surgical procedure(s) performed
- Date/time of OR entry
- Date/time of anesthesia induction
- Date/time of surgery start
- Date/time of cardiopulmonary bypass start
- Date/time of aortic cross-clamp
- Date/time of aortic cross-clamp removal
- Date/time of cardiopulmonary bypass end
- Estimated blood loss
- IV fluid administered
- Blood transfused

10.3 Postoperative data

- Date/time of ICU admission
- Date/time of extubation

- Date/time of ICU discharge
- Date/time of hospital discharge
- Vasopressor (norepinephrine, vasopressin) use at ICU admission
- Inotrope (dopamine, epinephrine, milrinone, dobutamine) use at ICU admission
- Pacemaker use at ICU admission
- Date/time of first AF
- Presence of rapid ventricular response with first AF
- Heart rate at time of AF diagnosis
- Heart rate at initiation of study group treatment (initial amiodarone bolus)
- Hourly heart rate for 24 hours, beginning at start of study group treatment
- Date/time of study randomization
- Date/time of first study drug administration
- Total number of amiodarone boluses administered
- Restoration of normal sinus rhythm by ICU discharge
- Restoration of normal sinus rhythm by hospital discharge
- Date/time of normal sinus rhythm
- Total number of stable AF episodes (excluding initial episode) prior to ICU discharge
- Total number of stable AF episodes (excluding initial episode) prior to hospital discharge
- Presence of hypotension (SBP < 90 mmHg or increase in vasopressor infusion by 1.5x to achieve SBP > 90 mmHg) after amiodarone therapy during amiodarone IV load period
- Severity of hypotension after amiodarone therapy during amiodarone IV load period
    - Mild: No intervention needed
    - Moderate: Hypotension resolved after fluid bolus

    - Severe: Hypotension requiring vasopressor or inotropic therapy
    - Very Severe: Hypotension requiring multiple vasopressor or inotropic therapies
- Presence of bradycardia (HR <60 beats per minute) after amiodarone therapy during amiodarone IV load period
- Presence of conduction abnormality during amiodarone IV load period
- Severity of conduction abnormality during amiodarone IV load period
    - Mild: No intervention
    - Moderate: Temporary pacemaker required for ≤ 12 hrs
    - Severe: Temporary pacemaker required for 12-48 hrs
    - Very Severe: Temporary pacemaker required for ≥ 48 hrs or permanent pacemaker required
- Presence of pulmonary fibrosis related to amiodarone therapy
- Severity of pulmonary fibrosis related to amiodarone therapy
    - Mild: No intervention needed
    - Moderate: Discharged on oxygen at night only
    - Severe: Discharged on continuous oxygen
    - Very Severe: Discharged on mechanical ventilation or patient death due to pulmonary fibrosis

11. STATISTICAL ANALYSIS PLAN

Because the effect size of the RBDR regimen is unknown, a sample size calculation was not completed. After all research procedures have been completed for 60 subjects (30 subjects in

each treatment group) that have been randomized, the primary outcome analysis will be performed as described below. If there is a clinically-significant and a statistically-significant finding in the primary outcome analysis, defined as a p-value <0.05, the study will be closed and all statistical analyses described below will be completed. If there is a clinically-significant but not statistically significant finding in the primary outcome analysis, defined as a p-value between 0.05 and 0.10, the study will be extended to randomize another 20 subjects. Following the recruitment of these additional 20 subjects, the study will be closed and all statistical analyses described below will be completed. If there is neither a clinically-significant or statisticially-significant finding in the primary outcome analysis, defined as a p-value > 0.10, the study will be closed and all statistical analyses described below will be completed.

11.1 Baseline and demographic data

To describe baseline and demographic data, preoperative, intraoperative and postoperative data will be summarized and compared between patients randomized to the CDR and RBDR groups. Binomial and categorical data will be described as number (N) and percentage. Continuous data will be analyzed for normality. Data will be tested for normality using the Shapiro-Wilk test. Normal data will be described by the mean and standard deviation; whereas, non-normal data will be described by the median and interquartile range. Nominal data will be compared with the Fischer's Exact test or the Chi-Square test, as appropriate. Normal continuous data will be compared with the 2-tailed, student t-test. Non-normal continuous data will be compared with the Mann-Whitney U test. All results with $p<0.05$ will be considered significant.

11.2 Primary Objective

To assess the primary objective, the number and percentage of patients in each group who have converted to NSR after 24 hours will be calculated. The number of patients who convert to NSR in each group will be compared with either the Fischer's Exact test or the Chi-Square test, as appropriate.

11.3 Secondary Objectives

To assess the secondary objectives, the following statistical analysis plan will be used:

- To compare the total time, in minutes, during the first 24 hours that the patient achieves target HR (HR < 110) between groups, first, the time that each patient has the target HR will be calculated. The total time at target HR will be calculated as the number of hourly HR measures ≤ 100 x 60 minutes. This calculated time data for each group will be will be analyzed for normality. Normal data will be described by the mean and standard deviation; whereas, non-normal data will be described by the median and interquartile range. If one group is normal and one group is non-normal, both groups will be reported as non-normal data. The total time at target HR between groups will then compared with either the 2-tailed, independent samples student t-test (normal data) or with the Mann-Whitney U test (non-normal data).

- To compare the time to achieve target HR (HR ≤ 110 bpm) between patients in each group, the time to achieve target HR will be calculated for each patient. This time will be calculated as the total time, in minutes, between the start of the initial amiodarone bolus and the first recorded HR ≤ 110 bpm. The time to achieve NSR data will be analyzed for normality. Normal data will be described by the mean and standard deviation, whereas

non-normal data will be described by the median and interquartile range. If one group is normal and one group is non-normal, both groups will be reported as non-normal data. The time to achieve NSR will then compared with either the 2-tailed, independent samples student t-test (normal data) or with the Mann-Whitney U test (non-normal data).

- To compare the time to achieve NSR between patients in each group, the time to achieve NSR will be calculated for each patient. For patients who do not convert to NSR by the time they are discharged from the hospital, the date/time that they achieve NSR will be the date/time of hospital discharge. The time to achieve NSR data will be analyzed for normality. Normal data will be described by the mean and standard deviation, whereas non-normal data will be described by the median and interquartile range. If one group is normal and one group is non-normal, both groups will be reported as non-normal data. The time to achieve NSR will then compared with either the 2-tailed, independent samples student t-test (normal data) or with the Mann-Whitney U test (non-normal data).

- To compare the percentage of patients who achieve NSR by ICU discharge and hospital discharge, the number of patients in each group who have converted to NSR at each time point will be calculated and reported as number and percentage. The number who have achieved NSR will be compared with the Fischer's Exact test or the Chi-Square test, as appropriate.

- To compare the percentage of patients who have recurrent AF before ICU discharge and hospital discharge, the number of AF episodes after the initial AF episode will be counted

for each patient in each group prior to ICU discharge and prior to hospital discharge. The mean (normal data) or median (non-normal data) number of additional AF episodes will be compared between the groups using the 2-tailed, independent samples student t-test (normal data) or with the Mann-Whitney U test (non-normal data).

- To compare the incidence and severity of hypotension, the number of patients who develop hypotension will first be calculated and reported as number and percentage. The number of patients with hypotension will be compared with the Fischer's Exact test or the Chi-Square test, as appropriate . The number of patients who develop mild, moderate, severe or very severe hypotension will then be calculated and reported as number and percentage. The number of patients with each severity class will then be compared between groups using Somers' D test for ordinal data.

- To compare the incidence and severity of conduction abnormalities, the number of patients who develop bradycardia will first be calculated and reported as number and percentage. The number of patients with bradycardia will be compared with the Fischer's Exact test or the Chi-Square test, as appropriate. The number of patients who develop mild, moderate, severe or very severe conduction abnormalities will then be calculated and reported as number and percentage. The number of patients with each severity class will then be compared between groups using Somers' D test for ordinal data.

11.4 Exploratory Objectives

- To evaluate preoperative, intraoperative and postoperative factors that affect the efficacy of the amiodarone dosing strategy in achieving NSR at 24 hours, ICU discharge and hospital discharge, multiple variable logistic regression modeling will be constructed using any significant variable discovered in the bivariate analysis.
- Evaluate preoperative, intraoperative and postoperative factors that affects the safety profile of the repeated amiodarone bolus dosing regimen, multiple variable logistic regression modeling will be constructed using any significant variable discovered in the bivariate analysis.

12. RESOURCES

All usual care for a post-operative surgical patient will be provided to enrolled patients by hospital staff. Emergency medical equipment, medications, and supplies will be at the physician's disposal should the patient have an acute, unexpected reaction to study drugs. The anesthesiology critical care team will be responsible for ordering study-related drugs, according to standard of care protocols, and for responding to unexpected reactions to study drugs. Evaluations, examinations, and tests will be ordered by the cardiovascular surgery, anesthesiology critical care medicine or other consultants according to standard of care protocols. Research staff of the Anesthesiology Research Program will be responsible for randomizing enrolled patients, communicating group assignment to the anesthesiology critical care medicine team, monitoring study-related complications and adverse events, and collecting study-related data.

13. POTENTIAL RISKS

Because this study compares 2 amiodarone dosing strategies already used in the proposed study population, there are no specific study-related risks of amiodarone administration. Regardless of whether they are enrolled in this study, patients with persistent, postoperative stable AF will receive amiodarone IV bolus and infusion, unless they have a contraindication to its uses. These patients may receive either the CDR or the RBDR, based entirely on clinician preference. In this study, we are comparing the efficacy and safety of the currently used dosing regimens.

The primary risk of this study is, therefore, only a risk of breach of confidentiality.

14. SAFETY PRECAUTIONS

14.1 Risks from Breach of Confidentiality

All enrolled patients will be given a 3-digit study identification number (SID) at the time of study enrollment. All patient data will be identified only with the SID and will be maintained only on the REDCap online database. All informed consent records will be scanned in the Department of Anesthesiology, stored on the REDCap online database, and then immediately destroyed in the Department of Anesthesiology in a paper shredder.

15. BENEFIT VERSUS RISK

Patients enrolled in this study may receive a direct benefit from their enrollment or randomization to either group. The risk in this study will be the same across both groups.

16. AVAILABLE ALTERNATIVE TREATMENT

For patients that do not consent to enrollment in this study, they will receive current standard of care treatment for stable, postoperative AF, as determined by the cardiovascular surgery and/or anesthesiology critical care medicine teams.

17. RESEARCH MATERIALS, RECORDS, AND PRIVACY

The research team maintains the right to keep, preserve, use and dispose of the findings from this study. Research records from this study will be maintained in a confidential manner; subjects' names will not be associated with any study procedures or published results. All data will be used for the purpose of research. All data will be retained for six years after study closure. Electronic records will be deleted at the specified times according to UK policy A13-050.

18. CONFIDENTIALITY

All electronic data containing identifiers will be stored on the secure REDCap database. Only designated study personnel will have access to data files. Investigational records for this study will be maintained in a confidential manner; subjects' names will not be associated with any published results nor used for any purpose. All data will be used for the purpose of research. All data will be retained for six years after study closure.

19. PAYMENT

No financial compensation will be provided to subjects.

20. COSTS TO SUBJECTS

The patient, the patient's insurance company, Medicare, or Medicaid will be responsible for the costs of all care and treatment that they receive during this study, including the cost of the study drug. Because both amiodarone dosing regimens are currently used, the cost of the study drug and other costs are considered medically reasonable and necessary and will be part of the care the patient would receive if they did not take part in this study.

21. DATA AND SAFETY MONITORING

Each subject will be monitored for adverse events (AE) and serious adverse events (SAE) by the PI and/or a member of the research team. Because hypotension and conduction system abnormalities are expected, reversible and treatable complications of amiodarone, they will be monitored but will only be considered AE if they reach "severe" criteria and will only be considered as SAE if they reach "very severe" criteria. Other known complications of amiodarone therapy will be reported as AE or SAE, as appropriate. All AE and SAE will be reported to the IRB per IRB guidelines.

The PI and co-investigators will review the AE and SAE reports after the first 10 patients have completed the research protocol to evaluate patient safety. If, after the first 10 patient have been evaluated, there were no AE or SAE reported, the PI and clinical co-investigators will continue to review the AE/SAE reports after every additional 20 patients have completed the protocol. If, during these periodic reviews, there are reported AE or SAE, the PI and clinical co-investigators will consider whether to continue patient enrollment and study procedures based on an assessment of benefit versus risk. The PI will have the responsibility, in consultation with the

clinical co-investigators, to decide whether to continue the study at each 20-patient interim safety analysis. The PI will inform the IRB if study procedures will be terminated.

22. SUBJECT COMPLAINTS

If patients have complaints in relationship to their participation in this research study, they may contact the staff in the University of Kentucky (UK) Office of Research Integrity (ORI) between the business hours of 8am and 5pm EST, Monday-Friday at 859-257-9428 or toll free at 1-866-400-9428.

23. RESEARCH INVOLVING NON-ENGLISH-SPEAKING SUBJECTS OR SUBJECTS FROM A FOREIGN CULTURE

Not Applicable.

24. HIV/AIDS RESEARCH

Not Applicable.

25. APPENDICES

None.