Use of intravenous amiodarone after coronary artery bypass grafting to reduce the incidence of post-operative atrial fibrillation

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A. Introduction

a. Rationale

Atrial fibrillation occurs after coronary-artery bypass grafting (CABG) in about 20-50% of patients. It has been shown to increase morbidity, prolong hospital stay, and increase cost of hospitalization. There is as of yet no consensus among physicians as to whether routine prophylaxis should be given or what agent should be used if prophylaxis is to be done. Studies with agents such as beta-blockers, calcium-channel blockers, and digoxin have failed to demonstrate consistent benefit when weighed against their side effect profiles, although beta-blockers have shown the most promise. A drug that has recently been studied for this use is amiodarone. If it can be demonstrated to reduce the incidence of atrial fibrillation in post-CABG surgery patients with an acceptable side-effect profile, it should decrease morbidity and reduce length of stay and cost of hospitalization.

b. Hypotheses

Amiodarone given intravenously after CABG is effective in decreasing incidence of atrial fibrillation prior to discharge. As a secondary hypothesis, it also reduces length of hospitalization and cost of hospitalization.

B. Methods

a. Conceptual and Operational Definitions

Atrial fibrillation - atrial fibrillation rhythm as determined by a single cardiologist experienced in interpreting ECGs. Participants in the trial will undergo continuous EKG monitoring (whether in an ICU or step-down unit). The same cardiologist will review all rhythms suspected to be AF AF will not be said to have occurred for the purposes of the study unless it lasts at least 10 minutes or requires treatment for symptoms or hemodynamic instability.

Length of hospitalization - this will be determined from the time of admission to the time of death or discharge from hospital.

Cost of hospitalization - this will be based on determination of cost by the NYP Budget Office. The amiodarone arm will include the cost of the drug administered. IV Amiodarone 150 mg/3 ml is approximately $84.03.

Duration of AF - total # of minutes in AF from during hospital admission as determined by telemetry software.

Mean AF Ventricular rate - Mean ventricular rate in AF, as determined by telemetry software.

Morbidity and Mortality - Mortality defined as all-cause mortality during hospital stay and morbidity as occurrence of acute renal failure, cerebrovascular accident, pneumonia, ventricular fibrillation/tachycardia, major gastrointestinal bleed, or myocardial infarction.

b. Study Design

This will be a prospective, interventional study. Patients will be randomized to either amiodarone treatment or placebo. Both patients and investigators will be blinded. c. Statistical Analysis Data were analyzed according to the intention to treat principle. Continuous variables will be presented as mean ± SD and compared between treatment groups using the student's t-test. Discrete variables will be compared using the chi-square test. KaplanMeier analysis with the log-rank test will be used to compare the

probability of atrial fibrillation in both groups. A p value of less than 0.5 will be considered statistically significant.

c. Sample Size

Sample size was determined as follows: $n = \frac{8\ p_1q_1}{effect^2} + \frac{p_2q_2}{effect} + 2 + 2 = 283$

Where p_1 (incidence of AF in controls) is assumed to be *30%* and P_2 (incidence of AF given *35%* treatment effect) is *19.5%.* This assumes an alpha of *0.05* and power of *0.80.*

C. Subjects Selection

Participants entering the study will be drawn from those undergoing elective CABG at this center. After obtaining consent of the treating physician(s), prospective participants will be approached during standard pre-admission testing and eligibility for the study determined. Written informed consent will be obtained from all participants.

Exclusion Criteria

- Age < 20 years
- VaIvular surgery or surgical technique other than standard midline sternotomy
- Other concurrent surgery
- Past history of atrial fibrillation
- Taking Class I or III antiarrhythmics
- Contraindications to amiodarone (i.e. atrioventricular conduction disease (<1 block), sick sinus syndrome, thyroid disease (uncontrolled hypothyroidism/hyperthyroidism), interstitial lung disease (FVC>50% predicted), renal (creatinine >1.5) or liver disease (AST or ALT greater than 2x upper limit normal)
- Emergency surgery

Patients who consent to the study and who do not meet any of the exclusion criteria above will be randomized to either amiodarone or placebo. Note that patients on calcium-channel blockers, beta-blockers, and digoxin are eligible for enrollment so long as these drugs were not started with the intent to prevent AF Patients who arrive at the ICU in atrial fibrillation, an IABP, or *2* cardiac indexes *<2.0* L/min/M2 (done by thermodilution technique 4 hours apart) will not be given amiodarone but will be analyzed in the group into which they were randomized.

D. Study Procedures/Miscellaneous

Upon arrival to the ICU after CABG surgery participants are given either intravenous amiodarone or placebo formulation. Goal is to initiate therapy within 2 hours, except in those patients in whom cardiac index is being followed to assess eligibility for infusion. Neither treating physicians nor nurses were aware which agent a patient was scheduled to receive. Dosing of amiodarone included a standard loading dose followed by 0.5 mg/min infusion as used for prevention of ventricular arrhythmias. The infusion was continued for a total of 3 days after initiation. Most studies show that the highest incidence of AF occurs 2-3 days post-surgery. Patients who were randomized and then subsequently met one of the exclusion criteria or in whom the drug was discontinued for some reason were analyzed in their initial group according to the *intention to treat principle.*

The side effect profile of amiodarone includes heart failure, AV nodal block, hepatotoxicity, and pulmonary toxicity. However, many of the side effects occur with chronic administration and all trials in

settings similar to this study have not shown any increased morbidity or mortality in amiodarone-treated patients compared to placebo. Bradycardia was not considered a reason to discontinue the drug since all patients had internal atria[and ventricular pacing wires placed during surgery.

Since beta-blockers have been shown in some studies to be effective in the prophylaxis of AF, it is felt that an attempt should be made to ensure similar rates of their use in the 2 arms so as to isolate the effect of amiodarone. Other studies have shown that use of both beta-blockers and amiodarone may be more effective than either drug alone.

There will be neither additional cost to subjects for participation in the study nor any compensation for participating in the study.