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Peri-operative Amiodarone in Cardiac Surgery Patients at High Risk for Post-Operative Atrial Fibrillation, Clinical and Economic Analysis

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Peri-operative Amiodarone in Cardiac Surgery Patients at High Risk for Post-Operative Atrial Fibrillation, Clinical and Economic Analysis

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Thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
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For the MSc degree in Epidemiology

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Abstract:

Atrial fibrillation (AF) affects up to 50% of post-operative cardiac surgery patients. AF is rarely fatal and most cases are transient and clinically benign. AF however could occasionally lead to many serious complications such as thromboembolic strokes, ischemic bowel, hypotension, or hemorrhage secondary to the required anticoagulation therapy. In addition, hospital length of stay is often prolonged due to the need to control this arrhythmia prior to discharge. Many strategies to prevent the onset of this condition have been the subject of intense research in recent years. Many pharmacologic and non-pharmacologic agents have been studied with varying degrees of success. Amiodarone, a very effective class III anti-arrhythmic agent, has been shown to reduce the onset of this condition by half in this patient population. Most Amiodarone studies were conducted on coronary artery bypass grafting (CABG) patients and the uptake of this intervention strategy by clinicians has been poor at best. The purpose of this study was to examine the possible benefit of using Amiodarone in a select group of cardiac surgery patients who were deemed to be at a higher risk of developing post-operative AF using a randomized controlled trial model. This select group of patients included valve patients, patients with poor left ventricular function, and the elderly. In addition, the possible economic benefit of such selective prophylactic strategy was evaluated. No clear clinical or economic benefits were demonstrated at the conclusion of the trial. The required a priori sample size was not achieved at the conclusion of the trial and hence many of the results did not achieve statistical significance.

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1.0 Introduction:

Atrial fibrillation (AF) is an arrhythmia that is very commonly encountered after cardiac surgery. Various reports indicate that the incidence of this condition is approximately 25 to 50% in cardiac surgery patients post-operatively (1,2,3,4,5,6). Certain patient populations are more predisposed to develop such arrhythmia. This includes patients with poor cardiac function, the elderly, and patients undergoing valve procedures (7,8,9). This arrhythmia is responsible for increased morbidity but seldom mortality (10-14). AF leads to increased risk of thrombo-embolic events such as strokes, ischemic colitis, and acute limb ischemia (10,11). In addition, hemodynamic instability due to AF is common in patients with poor cardiac functions. This instability is due to losing the atrial contribution to cardiac output given the fibrillating, non-contracting status of the atria. Current guidelines recommend the institution of anticoagulation in AF lasting greater than 48 hours in duration in order to reduce AF-related thromboembolic complications (15). The requirement for such anticoagulation however is known to increase the risk of bleeding complications including hemorrhagic strokes and gastrointestinal bleeds which could lead to significant morbidity, disability and sometimes mortality (10,13,14). Moreover, AF increases post-operative length of hospital stay in many patients leading to increased health care costs in addition to compromising patients' quality of life (2,12). Hospital discharge is frequently delayed in patients suffering from post-operative AF in order to either treat this condition or to institute anticoagulation due to refractory AF (lasting more than 48 hours). The need for anticoagulation prior to hospital discharge takes an average 2 to 3 days to achieve. Earlier discharge is possible with the use of home-based anticoagulant injections (low molecular weight heparin) in certain situation albeit with added cost.

Multiple strategies to treat this arrhythmia when it occurs are utilized with various degrees of success (16-30). Patients who experience AF, either in the general population or in the post-operative population, are treated with a variety of medications such as beta-receptor blockers, digoxin, and calcium channel blockers in order to control the AF-related tachycardia (rate control strategy). In addition to controlling the AF-related tachycardia, a variety of well-established anti-arrhythmic therapies such as sotalol, Amiodarone, and electrical cardioversion have also been utilized to revert AF patients to normal sinus rhythm (rhythm control strategy). Unfortunately, some patients remain in AF despite all these treatment maneuvers and therefore require anticoagulation to prevent the development of thrombo-embolic events as a consequence of prolonged AF (10). No difference in mortality was demonstrated by using either method of treatment (rate vs. rhythm control). The AFFIRM trial by Wyse et al reported a small and statistically insignificant 2.5% difference in mortality in 4060 AF patients randomized to be treated using either the rate or rhythm control methods (16).

Given the magnitude of this problem, an active prevention strategy seems more logical and appropriate. The cost to patients form a clinical and psychological stand point in addition to the possible increased economic costs due to AF treatment and possible AF-related complications warranted the development of a prophylactic therapy rather than a more passive approach of treating this arrhythmia after it develops.

The purpose of this project was to review the literature searching for available evidence supporting the use of various prophylactic agents to reduce the rates of post-operative AF in cardiac surgery patients and to conduct a study to examine the benefits of using the anti-arrhythmic agent, Amiodarone, in reducing the incidence of AF in a select

group of cardiac surgery patients deemed to be at a higher risk to develop this arrhythmia. This preventative intervention may decrease patient morbidity and mortality and possibly lead to reduced hospital costs associated with treating this condition.

2.0 Review of the Literature:

Several studies have evaluated the role of prophylactic therapy in reducing the incidence of post-operative AF in cardiac surgery patients (1,2,5,6,12,31,32-). Preventative interventions may decrease patient morbidity and mortality at relatively little cost. Potential therapies examined included class I anti-arrhythmic agents (e.g. procainamide), class II anti-arrhythmic agents (beta receptor blockers), class III agents (e.g. Sotalol, Amiodarone), digitalis, or peri-operative bi-atrial pacing to reduce the risk of post-operative AF. To date, these interventions have only been moderately effective.

2.1 Procainamide for AF prophylaxis in Cardiac Surgery Patients:

A randomized trial compared the effect of prophylactic peri-operative procainamide (Class I anti-arrhythmic) on the incidence of post-operative AF (1). Peri-operative procainamide was associated with a decrease, albeit statistically insignificant, in the number of patients who developed post-operative AF (37.5% compared to 18%). However this treatment led to an unexpected increase in hospital length of stay by 2 days. Procainamide is associated with hypotension, especially if infused rapidly. Many clinicians are wary of using this agent due to its poor safety profile.

2.2 Beta-receptor blockers for AF prophylaxis in Cardiac Surgery Patients:

Beta-blockers (class II anti-arrhythmics) are widely used in cardiac patients for a variety of reasons. Beta-blockers are the most widely used prophylactic agents for AF prophylaxis in cardiac surgery patients (6,33,34). This is mainly due to the fact that most of these patients need to be on such agents due to the existence of coronary artery disease for which beta-

blockers are used to reduce the risk of myocardial infarctions and death (35,36). For instance, Stephenson et al demonstrated a statistically significant reduction in AF episodes from 23% to 10% in 223 patients undergoing coronary artery bypass grafting randomized to receive either propanolol or placebo ($P < 0.05$). A recent meta-analysis by Crystal et al (37) demonstrated a statistically significant reduction of AF in cardiac surgery patients with the use of various beta-blocker agents (OR 0.35, 95% CI 0.26 to 0.49). Only randomized controlled trials were included in this meta-analysis. Given the available evidence the latest American Heart Association (AHA) guidelines in 2004 recommended the use of beta-blockers before and after cardiac surgery to reduce the incidence of AF post-operatively (38).

2.3 Sotalol for AF prophylaxis in Cardiac Surgery Patients:

Sotalol is a special beta-blocker that has both class II and class III anti-arrhythmic properties. Gomes et al reported a significant reduction in post-operative AF (38% vs. 12.5%) with the use of sotalol peri-operatively compared to placebo (5). Unfortunately the patients in the treatment and control groups were not equal at baseline. Patients in the sotalol group were 9 years younger than the controls, and less of them had valve surgery. It's well known that both older age and valvular surgery increase the risk of post-operative AF which might account for the different AF rates between the control and experimental groups rendering the results difficult to interpret (7,8,9). Furthermore, many surgeons are reluctant to use sotalol due to the small but serious risk of malignant ventricular arrhythmias (Torsade de pointes).

2.4 Digoxin for AF prophylaxis in Cardiac Surgery Patients:

Digoxin is utilized to control the rate of atrial tachy-arrhythmias given its blocking effects on the atrio-ventricular (AV) node in the heart. Various studies have evaluated the possible benefit of this agent to prevent post-operative AF in cardiac surgery patients (39,40,41). No benefit was found however. Kowey et al conducted a meta-analysis in 1992 that examined the effectiveness of digoxin in the prevention of post-operative atrial tachy-arrhythmias (AF or atrial flutter) in patients undergoing coronary artery bypass grafting (41). The incidence of these arrhythmias in the digoxin group and the placebo group was 17.6% vs. 19% respectively. Yazicioglu et al in 2002 randomized a group of CABG patients to receive either a combination of digoxin and atenelol (a beta-blocker) or digoxin alone or atenelol alone or placebo pre-operatively and evaluated the incidence of post-operative AF (42). Post-operative AF affected only 5% of patients who received pre-operative combined digoxin and atenelol compared to 25% of the placebo patients (P=0.012). The difference between the placebo group and the digoxin only or atenelol only groups was not statistically significant (15.4% vs. 17.9%, vs. 25% respectively). Therefore peri-operative digoxin therapy alone was found to be ineffective in preventing post-operative atrial arrhythmias after coronary surgery.

2.5 Bi-Atrial Pacing for AF prophylaxis in Cardiac Surgery Patients:

A number of studies have examined the benefit on non-pharmacologic options, such as over drive pacing, to reduce the risk of post-operative AF in cardiac surgery patients. Greenberg et al have demonstrated a reduction in AF from 38% to 8% in cardiac patients assigned to pacing (right atrium or left atrium or bi-atrial pacing) vs. no pacing (43). Most studies

unfortunately did not demonstrate any economic benefit of such prophylactic treatment. Gerstenfeld et al examined the effect of prophylactic bi-atrial pacing on the incidence of post-operative AF in coronary artery bypass patients (31). That study showed that despite the safety of this therapy, AF episodes did not decrease post-operatively (32.5% compared to 33%).

2.6 Magnesium for AF prophylaxis in Cardiac Surgery Patients:

Magnesium supplementation may reduce the risk of post-operative AF in cardiac surgery patients. Various randomized trial examined the possible benefits of such supplementation (44-46). Kaplan et al randomized 200 consecutive coronary bypass patients to receive either intravenous magnesium supplements or placebo (44). A significant relationship was found between low magnesium sulfate levels and increased incidence of AF ($P < 0.05$). The incidence of postoperative AF however was similar in the magnesium and control groups, 15% and 16% respectively ($P > 0.05$). In addition, no significant difference was found between operations conducted using cardiopulmonary bypass support and non-cardiopulmonary bypass support (beating-heart) in terms of AF ($P > .05$). AF led was shown to extend the duration of hospital stay as expected. On the contrary, Toraman et al (45) demonstrated the benefit of magnesium supplementation in reducing the incidence of post-operative AF in 200 coronary artery bypass patients utilizing a randomized-controlled trial model as well. The rate of AF was only 2% in the magnesium group vs. 21% in the control group ($P < 0.001$). Hazelrigg et al (46) randomized 202 coronary bypass patients to receive either magnesium supplements or placebo peri-operatively. The incidence of post-operative AF was 30.5% vs. 42.3% in the magnesium and control groups respectively ($P = 0.08$). In a

recent meta-analysis of 16 trials the rate of post-operative AF was significantly reduced in magnesium treated patients compared to placebo patients (47). AF affected 23% vs. 31% of patients (RR 0.77). No difference in length of hospital stay or mortality was found however. That study also revealed a large heterogeneity among the studies in terms of size and effect and there was also a suspicion of publication bias. Therefore, the use of magnesium supplementation routinely in cardiac surgery patients to reduce post-operative AF remains unsupported and not advised.

2.7 Statins for AF prophylaxis in Cardiac Surgery Patients:

Statins are widely used in patients with coronary artery disease due to well-documented long-term survival benefits (48,49). These agents may also reduce the rates of AF post-operatively. Mozaffarian et al demonstrated the benefit of statins peri-operatively in coronary artery patients who were not on statin agents prior to surgery (48). A total of 200 coronary patients were randomized to receive either atrovastatin 40 mg daily or placebo. AF affected 35% of statin treated patients compared to 57 of placebo treated patients. Statins are already widely used in all patients however. Almost all cardiac patients are placed on these agents and therefore no added benefit would be achieved from studying these agents as possible AF prophylactic drugs.

2.8 Amiodarone for AF prophylaxis in Cardiac Surgery Patients:

Recent studies revealed that the class III anti-arrhythmic agent, Amiodarone, appears to reduce the risk of post-operative AF by half in cardiac surgery patients undergoing mostly coronary artery bypass grafting (2,50-59). Unfortunately many of those studies were not

randomized in design. Several recent randomized trials utilizing amiodarone as a prophylactic agent in cardiac surgery patients have been conducted however. A recent meta-analysis of 10 randomized controlled trials that randomized a total of 1744 cardiac surgery patients to receive either amiodarone or placebo demonstrated a significant reduction in the incidence of post-operative AF in these patients (RR 0.64, 95% CI 0.55-0.75) (58). The vast majority of patients in these trials were coronary artery bypass patients however. Three of the trials used intravenous amiodarone (52,53,54) while the rest used oral amiodarone (2,55,56,57). Only one randomized trial demonstrated a reduction in cost and hospital length of stay with such prophylactic treatment however (2). Intravenous Amiodarone is more costly than oral Amiodarone, which might account for the negative economic benefit in many of these trials. The rates of strokes were also reduced in the amiodarone group (RR 0.39, 9%CI 0.21-0.76), and length of hospital stay was also reduced albeit it was not statistically or clinically significant (weighted mean difference –0.63 day, 95%CI –1.03 to –0.23 days). All studies reported adverse events, but none of them indicated how these events were assessed. Furthermore, 3 studies found significantly more adverse events with amiodarone therapy, including nausea, bradycardia, and increased intensive care monitoring and support. Not all studies used ß-blockers routinely, and the amiodarone regimens were not uniform among trials (different doses and treatment duration). Very few trials met the stringent inclusion criteria and none of them reported completeness of follow-up. Following the publication of that meta-analysis, another randomized trial assessing the effect of peri-operative amiodarone on the incidence of post-operative AF in cardiac surgery patients was presented and published in 2005 (57). This trial is considered to be the largest thus far. This was a double-blind randomized trial of 601 patients undergoing elective coronary artery

bypass graft surgery and/or valve replacement/repair surgery between 1999 and 2003. The patients were followed up to 1 year. The trial utilized oral amiodarone (10 mg/kg daily) or placebo administered 6 days prior to surgery through 6 days after surgery (total of 13 days). Randomization was stratified for subgroups defined by age, type of surgery, and use of preoperative beta-blockers. Figure 1 shows the study design and patient assignments. Isolated CABG patients accounted for the majority (65%) of the total patient population. Atrial tachy-arrhythmias (Atrial fibrillation or Atrial flutter) occurred less frequently in the amiodarone patients (48/299; 16.1%) compared to the placebo patients (89/302; 29.5%). The overall hazard ratio (HR) was 0.52; 95% CI 0.34-0.69; P<0.001). This reduction was consistent in the various study strata. In patients younger than 65 years, atrial tachy-arrhythmias affected 11.2% of patients in the amiodarone group vs. 21.1% of patients in the placebo group (HR 0.51; 95% CI 0.28-0.94; P =0.02). In patients aged 65 years or older tachy-arrhythmias affected 21.7% of patients in the amiodarone group vs. 41.2% in the placebo group (HR 0.45; 95% CI 0.27-0.75; P<0.001). Patients who had CABG surgery only, amiodarone reduced atrial tachy-arrhythmias to 11.3% from 23.6% (HR 0.45; 95% CI 0.26-0.79; P =0.002); Patients who had valve replacement/repair surgery associated with or without CABG surgery, atrial tachy-arrhythmias afflicted 23.8% of amiodarone patients vs. 44.1% of placebo patients (HR 0.51; 95%CI 0.31-0.84; P =0.008). The concomitant use of amiodarone with peri-operative beta-blockers was also assessed in this study. In patients who received peri-operative beta-blocker therapy, atrial tachy-arrhythmias affected 15.3% of patients in the amiodarone group vs. 25.0% in the placebo group (HR, 0.58; 95%CI 0.34-0.99; P=0.03) while in patients who did not receive peri-operative beta-blockers tachy-arrhythmias affected 16.3% of amiodarone patients compared to 35.8% in the placebo group

(HR 0.40; 95%CI 0.22-0.71; P<0.001). There were no differences in serious postoperative complications such as in-hospital mortality, 1-year mortality or readmission to the hospital within 6 months of discharge. Patients receiving amiodarone however sustained more adverse cardiac events such as bradycardia (5.7 vs. 2%) and prolonged QTc interval on the electrocardiogram which is a known side effect of Amiodarone.

Amiodarone, albeit widely used and safe, is associated with a variety of side effects and complications including lung fibrosis, thyroid damage, skin photosensitivity, elevation in liver enzymes, bradycardia and hypotension. Most of these side-effects are associated with prolonged use however (months to years). This is almost never the case in this patient population. Given the relatively high cost of this agent and the few potential, albeit rare, side effects, a strategy of targeting all cardiac surgery patients is not likely to be efficacious or cost effective. This might account for the poor uptake of such strategy by clinicians. Consequently, a strategy of selectively targeting this treatment to patients at high risk for post-operative AF might be more clinically and economically appropriate especially if the cheaper oral amiodarone is utilized. Furthermore, this patient population is not only at higher risk for developing AF, but they could also suffer more consequences from complications related to AF given their poor reserve (especially patients with poor cardiac function or the elderly).

2.9 Factors that increase the risk of post-operative AF in cardiac surgery patients:

Various factors have been shown to increase the risk of post-operative AF in cardiac surgery patients. These factors include advanced age, valvular surgery, and poor ventricular ejection fractions (7,8,9). All published Amiodarone studies have either focused on coronary artery bypass patients or examined the effect of Amiodarone in preventing AF in all cardiac surgery patients without distinction to procedures performed. Most patients in those studies were also coronary artery bypass patients (2,53-57). These patients are generally at a lower risk for developing post-operative AF compared to patients undergoing more invasive procedures involving intra-cardiac interventions such as valve surgery. Unfortunately, no trial has attempted to selectively examine the efficacy, efficiency and cost-benefit of this prophylactic treatment in patients at higher risk of developing post-operative AF. Furthermore, it is not clear whether or not these high-risk patients actually benefit from, or be more resistant to, such prophylactic treatment. It is not apparent if the observed beneficial effects of prophylactic Amiodarone utilized in recent clinical trials were due to the small subset of high risk patients such as valve surgery patients or if most of the observed benefits were derived from the much larger coronary bypass population. Only 2 studies demonstrated the benefit of prophylactic Amiodarone in both CABG and valve patients, one was based on post-hoc subgroup analysis (2) but the other did stratify the patients based on procedure pre-operatively (57). It is well known that any type of post-hoc analysis is fraught with problems not the least being the fact that the patients were not randomized to belong to either of the comparison groups within the subgroups analyzed. Consequently, there has been some resistance among cardiac surgeons to use Amiodarone peri-operatively on all patients given

the relative high cost and inconvenience of such treatment and the vast number of patients undergoing cardiac surgical procedures.

As a result, we hypothesize that a strategy of prophylactic treatment with peri-operative oral Amiodarone targeted selectively to cardiac surgery patients at high risk for post-operative AF is more clinically and economically appropriate. Peri-operative Amiodarone should reduce the incidence and cost of post-operative AF in this patient population.

2.10 Conclusions:

Various agents have been found to reduce the incidence of atrial tachy-arrhythmias such as AF and atrial flutter in the cardiac surgery population. Most patients however were coronary artery bypass patients. These patients are at lower risk to develop this complication however. Many of these agents are used routinely in the cardiac surgery population at any rate due to a variety of reasons. Beta-blockers, for instance, are used in all coronary patients unless there is a contra-indication for their use. This is due to the fact that there is a survival benefit associated with the use of such agents in these patients (35,36). Despite this, the rates of AF are still very high in cardiac surgery patients. Amiodarone is used to treat active arrhythmias such as new AF or patients at risk of developing certain arrhythmias such as the malignant ventricular-based arrhythmias, ventricular tachycardia and ventricular fibrillation (20,21,60,61). However the uptake of Amiodarone by clinicians as a prophylactic agent for post-operative AF remains poor. The exact reasons for this remain uncertain. It could be due to the fact that it takes days to pre-load patients with this agent precluding its use in more

urgent cases, or the conflicting evidence regarding its clinical or economic benefits on hard end-points such as survival or reduced hospital length of stay.

The adoption of this preventative therapy might potentially be improved if it was directed against a selective group of patients who are either at a higher risk of developing post-operative AF or be harmed more by such arrhythmias compared to the average cardiac surgery patient.

3.0 Trial Rationale:

Given the high frequency of AF encountered during clinical practice, the concept of a proactive preventative measures became very appealing. Most surgeons have been hesitant to utilize any of the putative prophylactic interventions studied thus far. This is likely due to the considerable number of patients and associated increased cost with questionable clinical and economic benefits. Therefore, the concept of a more selective intervention targeting patients at higher risk of developing this arrhythmia such as valve patients, the elderly, or patients with poor cardiac function, could potentially be more beneficial and acceptable to clinicians. No such study exists so far however. Almost all patients studied have been coronary artery bypass patients who are generally at a lower risk of developing post-operative atrial arrhythmias such as atrial fibrillation or atrial flutter. Consequently the concept of designing such study was conceived and became the topic of this study and thesis.

Many possible interventions or agents could have been utilized to achieve this goal. Amiodarone is a common and powerful drug used to treat both atrial and ventricular arrhythmias such as AF and ventricular fibrillation (VF) respectively. As noted in Section 2.0, various studies have attempted to utilize this medication as a prophylactic agent to prevent AF in cardiac surgery patients. Most such studies demonstrated a reduction in the incidence of this arrhythmia but no mortality benefit. The lack of mortality benefit was not unexpected however given the low risk of death due to AF. Furthermore, only one of these trials demonstrated an economic benefit to such strategy (2). Many clinicians are hesitant to use other putative agents such as Sotalol due to the small but real risk of actually inducing arrhythmias (the fatal Torsade de Point type of ventricular arrhythmia). Other agents such as

beta-receptor blockers are already widely used in this patient population and almost all cardiac patients receive these agents at any rate. Despite this, 30-50% of patients still develop post-operative AF. Therefore, a more effective agent in addition to beta-blockers was required to further reduce the incidence of post-operative AF.

Amiodarone became the prime candidate given its well known efficacy in treating AF and relatively lower risk of side effects albeit definitely present (62,63) (Appendix A). This agent could be used either in an intravenous or oral forms. The cost of the intravenous form is greater and requires hospitalization to be administered. Consequently, the oral form was chosen. Amiodarone is a medication that has a large volume of distribution in the body and is taken up and stored by adipose cells. Consequently, a loading dose (5-10 grams) over many days is required prior to achieving a steady state blood drug level once the body cells are saturated with the drug. This therefore requires patients to start taking the medication days prior to surgery in order to achieve adequate blood levels to be effective.

Various epidemiologic study designs could have been utilized to demonstrate any possible benefit of Amiodarone in reducing the risk of post-operative AF in cardiac surgery patients. Observational study designs are burdened with the risk of reaching the wrong conclusions due to inherent design weaknesses. The results achieved from such studies could sometimes be affected negatively or positively by various known or unknown confounders stemming from imbalances between the groups of patients receiving the examined intervention of interest and patients receiving a placebo or any other comparative agent (poor internal validity). Of all available study designs, randomized controlled trials (RCTs) are deemed to be the most powerful and accurate in demonstrating any possible benefits related to any agent of interest. The randomization process in this study design

minimizes the differences in baseline known and unknown characteristics between the treatment groups and hence minimizes the effects of confounders. The randomization process ensures the internal validity of this study design by ensuring that each subject (patient) has an equal chance of being selected to be in the treatment or placebo group and hence minimize the differences in baseline characteristics. This minimizes the effects of any possible confounders on the observed results. Randomization could also be used to strengthen the external validity (generalizability) of the study by randomly selecting the sample from a population and therefore attempt to obtain a sample that closely resemble the population of interest. This is double-edged sword however. The inclusion and exclusion criteria could be so tight, that the results of such studies only apply to a small portion of the population. Many clinicians unfortunately extrapolate the results of such trials to include patients that were not included in the original trial. Many techniques are utilized within an RCT to reduce the risk of systematic error (bias) that could potentially skew the results of any trial and therefore risk obtaining inaccurate results. Some of these techniques include blinding both patients and study personnel to patients' group assignment. In addition, study protocols should be designed to be strictly followed by all subjects and to also ensure that the effects and outcomes are explicitly defined and measured using standardized techniques. These measures ensure that the observed effects of the agent of interest are not due to pre-conceived notions in patients or clinicians regarding any possible benefits of the intervention of interest. In addition this ensures that the observed effects are due to the intervention of interest only while controlling for all other variables that might also affect the results by ensuring that those variables (known and unknown) are equally distributed between the study groups.

Given all the benefits of RCTs compared to observational or other less powerful epidemiologic study models, this study design was selected for this project.

The benefits of RCTs come at a high cost however. These trials are fairly costly to conduct and usually require a relatively large number of subjects in order to minimize random errors in measurements (high power requirement). In addition, there is also cost associated with training the study personnel in order to minimize measurement bias and inappropriate patient allocation to the various study groups (selection bias). Also, unlike observational studies, RCTs involve the active addition or deletion of an agent or treatment of interest. This therefore requires the establishment of strict ethics guidelines that need to be stringently followed to ensure patient safety. Consequently the approval of the hospital ethics board was required in order to conduct this trial. Furthermore, patient adherence with the study protocol was also a concern and had to be strongly encouraged and monitored very closely. Adequate funding for this trial had to also be secured prior to starting this endeavor.

4.0 Study Objectives & Hypothesis:

4.1 Primary Objective:

To demonstrate the effectiveness of peri-operative oral Amiodarone in reducing the incidence of clinically important post-operative atrial fibrillation in cardiac surgery patients at high risk for developing this condition (valve patients; older patients > 65 years; or patients with poor left ventricular function, < 40% ejection fraction).

4.2 Secondary Objectives:

- To conduct an economic analysis in order to examine the impact on costs and outcomes of this treatment.
- To document all AF related complications up to 6 weeks post-surgery (Thromboembolic complications such as stroke, ischemic colitis and ischemic limbs; Myocardial infarction; bleeding from anticoagulation, death)

4.3 Study Hypotheses:

1) The use of prophylactic peri-operative oral Amiodarone reduces the incidence of post-operative AF in patients at high risk to develop this complication, namely, patients undergoing valve surgery or patients with poor left ventricular function (< 40% ejection fraction) or the elderly (age > 65 years).

2) The use of prophylactic amiodarone in the above patient populations leads to a reduction to AF-related side effects such as strokes, bleeding, or death.

3) The use of peri-operative Amiodarone in the above populations is cost effective.

5.0 Methods, Study Design & Patients:

This study was a double blinded, randomized controlled trial designed as follows:

5.1 Study population and recruitment procedure: The study population included all patients undergoing valve surgery who were due to have elective cardiac surgery at the Ottawa Heart Institute. These patients were deemed to be at high risk for post-operative AF. Inclusion and exclusion criteria are summarized in appendix B. All elective patients at the heart institute were triaged pre-operatively by one surgeon (TGM) prior to their assignments to the various surgeons. Most elective patients (67% of the total patient population) were routinely assessed for surgery in our pre-admission clinic approximately two weeks prior to the proposed day of surgery. Patients were approached by the study personnel for consent during the same pre-operative visit.

5.2 Description of intervention and control:

- Experimental group: This group received oral Amiodarone 400 mg twice a day starting 5 days pre-operatively, and continued for 5 days post-operatively (but at 400 mg daily). This dose was similar to those published by previous reports (2,18).

- Control group: This group received a placebo medication that looked identical to the treatment tablets (both were prepared by our hospital pharmacy).

Patients in both groups had their surgery as per usual clinical practice at our hospital with no changes. Rarely, a slight delay in the date of surgery occurred due to an emergency event.

When this problem was encountered, patients continued taking their study drugs and every effort was made to minimize such surgical delays (pills for extra 2 days were always included in the study bottles).

5.3 Allocation Procedure: A randomized double-blind controlled study was conducted over an 18 months period (2004-2006) in order to achieve the study objectives. Patients were randomized into the experimental group (receiving prophylactic amiodarone) or the control group (placebo). A stratified random design with block allocation was utilized to ensure that both arms of the trial include equivalent numbers of experimental and control patients in addition to the equal distribution of pre-operative beta-blocker use (Appendix C). Patients were initially stratified based on being on or off beta-blockers pre-operatively. Afterwards, patients were re-stratified into 3 subcategories (valves, older age, or poor ejection fractions). This resulted in 6 groups in total. Afterwards, patients were randomized to receive either Amiodarone or Placebo within each of their assigned stratum into using a pre-prepared block randomization sequence that was computer generated in the pharmacy. None of the study personnel was aware of the secret sequences. The block randomization ensured the equal distribution of patients in both arms of the study, namely Amiodarone and Placebo (Appendix D). An independent central unit (hospital pharmacy) was used for the randomization process. This unit was contacted to randomly assign each new patient to either the experimental or control arms of the study using the pre-prepared block randomization sequence. Patients and study personnel were blinded to the treatment assignments. Adherence to the study protocol, including the administration of study medications, was checked by myself personally throughout the study.

5.4 Outcomes:

- Primary Outcome (Primary End Point):

The primary end point of the study was the number of patients that developed "clinically important" AF post-operatively defined as any AF *leading* to an intervention. These episode included Stable AF lasting more than 5 minutes, leading to heart rates above 120 beats per minutes, or lasting more than 2 days and therefore requiring anticoagulation. Furthermore, clinically important AF included any unstable AF, such as AF leading to hypotension, shortness of breath, congestive heart failure, or requiring cardioversion (Appendix E). The initiation of the intervention to treat AF was determined according to a standard protocol (Appendix E). These interventions included increasing rate control medications, the use of anti-arrhythmic medications, electrical cardioversion, or anti-coagulation.

- Secondary Outcomes (Secondary End Points):

- Length of hospital stay and an economic analysis of this treatment regimen.
- The onset of *any* post-operative AF
- Total duration of all AF episodes per patient (with post-operative AF).
- Rhythm status on discharge
- AF and anticoagulation related complications; such as thromboembolic events or bleeding was documented. Standard definitions of transient ischemic attacks (neurologic events lasting < 24 hours) and stroke (neurologic deficit lasting > 1

week proven by clinical exam or computed tomography of the head) was be used. Bleeding is defined as bleeding requiring chest re-opening or any bleeding requiring blood transfusion post-operatively (As determined by the treating physicians). Bleeding was divided into events either due to anticoagulation or not since some bleeding could be surgical and not related to either anticoagulation or AF.

- Death.
- Post-operative myocardial infarction defined by the development of either new Q waves post operatively, or new ST elevation of > 1mm for more than 30 minutes or a maximum serum Troponin T levels of > 1.5 post-operatively.

Other potential confounders that could increase the risk of AF in these patients such as electrolyte disturbances, especially potassium, were also measured on multiple occasions (on days 0, day 1, 2, and 4 post-operatively).

5.5 Sample Size Determination:

Sample size for the trial was determined based on the primary end point of the study (Appendix F). Previous reports indicated that the incidence of post-operative AF in high-risk patients approached 50% (2). This was also the minimum clinical effect that our surgeons were willing to accept as the minimal clinical benefit to change their current practice habits. The rate of AF is approximately 40% in patients on beta-blockers. Assuming a 40% overall rate of clinically important AF in the control group and a 20% rate in the amiodarone group, a total of 162 patients (81 in each group) will be required to achieve a

power of 80% at an alpha error level of 5% (Appendix E). Previous reports have quoted a 10-18% withdrawal rate due to drug side effects (2,50-57). Consequently, 15 extra patients (18%) were required to be added to each arm of the study in order to compensate for this potential loss. Therefore, each arm of the trial needed to include 96 patients.

Approximately 1400 cardiac surgical procedures are performed at the Ottawa Heart Institute per year, 409 of which were valve cases. Most of these cases are elective, with about 67% of the patients assessed routinely at our pre-admission clinic. The average age of the patient population is approximately 66 years. Consequently, patient recruitment was expected to be complete within 12 months given the vast pool of available patients.

5.6 Standardized Study Procedures:

The actual treatment modality chosen to treat any post-op AF was determined by the clinical team. The initiation of treatment however was guided by the decision tree provided in Appendix E. The actual treatment modality chosen would not have affected the primary end-point of the study. Post operative AF would normally be treated with beta blockers, calcium channel blockers, or digoxin for rate control, or anti-arrhythmic medications or electrical cardioversion for reversion to normal sinus rhythm. No sotalol or other class III anti-arrhythmic agents, except Amiodarone, were allowed in order to minimize interaction between the various class III medications in case the patient was on Amiodarone. Intravenous Amiodarone boluses were allowed if deemed to be appropriate by the treating physician for difficult to control post-operative AF. The usual loading dose of Amiodarone for arrhythmia treatment is about 10 grams which is twice as high as our prophylactic study Amiodarone dose in case the patient was in the Amiodarone arm of the trial.

Anticoagulation for persistent AF (lasting more than 2 days) was initiated with intravenous heparin and then coumadin in order to minimize the risk of thromboembolic events unless there was contraindication to such treatment due to active or recent bleeding. This was done in compliance with the American Heart Association clinical practice guidelines (15).

In case anticoagulation with coumadin is initiated, a standardized coumadin protocol was used (loading with 2.5 mg daily for 3 days then measure and adjust the international normalized ratio "INR" to ensure acceptable levels as per our current practice, target INR 2 to 3). This protocol had been in use for over a year at our institution when the study was initiated.

The use of prophylactic overdrive pacing post operatively was not allowed given the theoretical chance that this might slightly reduce the risk of post-operative AF and therefore taint the study results.

5.7 Data collection and Safety Monitoring:

All enrolled patients were contacted 2 days after the initiation of treatment pre-operatively to ensure both adherence and the absence of adverse side effects. All pre- and post-operative complications were recorded and entered into a database. In addition, our study patients were continuously monitored post operatively for arrhythmias using telemetry for 7 days (or until the day of discharge whichever came first). Monitored Rhythms were always stored and were analyzed by the principle investigator for AF occurrence. AF was

defined as any episode requiring intervention as defined by our protocol (Appendix E). In addition, all the secondary end points were documented and analyzed.

Any adverse events that might have been attributed to amiodarone were closely monitored (bradycardia < 60 beats per minutes, decreased systolic blood pressure < 90 mmHg due to decreased heart rate, or allergic reactions). The development of any of these potential side effects led to the termination of the study drug (Amiodarone or placebo) and patient withdrawal from the study. This was done even though these side effects could also be due to other causes. Those patients were still followed however and all post-operative outcomes recorded. An exception to this was hemodynamically stable bradycardia in the first 2 days after surgery, which is very common and was easily remedied by the use of the routinely implanted temporary trans-thoracic pacemaker wires. When this bradycardia continued after the second post-operative day then the study drugs were terminated (Amiodarone or Placebo).

5.8 Ethics:

A formal application was made to the Ottawa Heart Institute Research Ethics Committee. The application included a copy of the proposed study with the objectives. It also included the exact patient inclusion and exclusion criteria. The source of funding was secured prior to Ethics submission (Physicians' Services Incorporated, PSI, Toronto, Ontario). All possible complications of Amiodarone were included in the proposal. Patient information sheets with consent forms are also designed and approved by the Ethics Board (Appendix G). The study adhered to the highest research ethics standards of the hospital and

was conducted after the approval of the Ottawa Heart Institute Research Ethics Board was obtained.

5.9 Economic Analysis:

The economic analysis was initially planned to include both differences in cost and differences in effect, if any were found (cost-effectiveness analysis).

The costs of surgery and capital cost (Hospital, clinic, operating room time) were deemed to be the same in both groups and therefore not collected or analyzed. Differences in nursing care costs are actually included in the differences in length of hospital stay. Physician fees are the same regardless of length of stay since post-operative care fees are included in the fee for surgery regardless of length of stay. The cost of any extra procedure required to either treat AF or its complication (such as the need for electric cardioversion to treat AF or endoscopy to investigate bleeding) was to be included in the cost part of the analysis equation. Increased costs due to catastrophic complications, such as strokes, would be accounted for by the increased hospital length of stay or post-discharge rehabilitation. The main differences in cost between the groups were therefore due to any differences in hospital days, ICU days, number of blood units transfused, and the cost of Amiodarone itself. More minor differences in drug costs such as differences in the utilization of the various standard cardiac meds among the patients were ignored since these patients received them anyways and the costs associated with them is considered to be very minor compared to the much greater overall hospitalization and surgical costs. Amiodarone was provided to the patients free of charge and was covered by the study grant. However it would be important to account for this since either patients or hospitals would have to provide this agent in case this prophylactic strategy was adopted by clinicians. The cost of 10 days of oral amiodarone is approximately $75 and is likely to drop in the future given the availability of cheap generic amiodarone.

The study plan was to utilize the difference in the primary outcome in order to determine an incremental cost effectiveness ratio: in this instance, the incremental cost associated with the reduction of one post-operative AF episode. This would have been performed if differences in the primary outcome were demonstrated. Uncertainty around costs was assessed through 95% confidence intervals. Uncertainty around the ICER was be assessed through 95% intervals obtained through non-parametric bootstrapping.

5.10 Statistical analysis:

Analysis was performed on an intention to treat basis. This analysis includes all patients enrolled in the study and took the study drugs, even if partially, or even if withdrawn form the study prior to completing the study medication regimen. This more conservative method of statistical analysis ensures that any statistically significant differences are actually real and due to the medication despite the dilution of any potential benefits by poor compliance or withdrawal from the study. Statistical analysis was performed using SAS 9.1 (SAS Inc, Cary, North Carolina). Student t-test for continuous variables and the Fisher exact or Chi-square analysis for Dichotomous variables were used to detect differences between the 2 groups. The Fisher's exact test was utilized in cases of small cell values (< 5) in the 2X2 tables. There was no interim analysis.

The frequency of the primary outcome was documented and reported. A dichotomous measure of the primary end-point was utilized using the first episode of clinically important AF as the event. Two outcome categories were used (post-operative AF, present or absent). Two exposure categories were used, control and amiodarone groups.

Chi-square analysis of the ensuing 2 X 2 table was used to test the statistical significance of the association between amiodarone use and the reduction in outcome events (AF).

Secondary end points were analyzed as follows:

- Average total duration of AF per patient in hours (continuous variable) was compared between the two groups of patients (control and amiodarone) and the student t-test was utilized to test for statistical significance.

- Chi-square analysis was performed to detect any association between treatment received and rhythm status on discharge from hospital (AF positive or negative).

- Adverse outcomes such as neurologic deficits (strokes), bleeding, myocardial infarction, and in-hospital death were reported as dichotomous variables (event present or absent) and chi-square analysis was performed in order to detect any statistically significant association between the treatment received and these outcomes.

- Average length of intensive care unit stay (in days) was compared using the student t-test between the two groups in order to detect any statistically significant differences.

- Average total length of hospital stay (in days) was compared using the student t-test between the two groups in order to detect any statistically significant differences.

- All blood work values on days 0,1,2, and 4 were recorded and compared using the student t-test. A "P" value of < 0.05 was used as significant in all analyses.

Figure 2 displays the time-line of the study.

6.0 Actual Study Conduct:

External funding was secured via the Physicians' Services Incorporated (PSI) in the amount of $20,000. In addition commitment from the division of cardiac surgery was made to provide clinic space and time for patient interviews and to aid in referring patients to the study.

All patients were screened during angiography or echo rounds as part of our clinical routine at the hospital. During this screening process, potential patients eligible for this study were flagged. Screening forms (Appendix G) were completed initially to determine if these patients meet the inclusion or exclusion criteria based on the available clinical information included in the consult forms. These patients were booked to be seen in clinics in order to meet the various surgeons as part of their pre-operative assessments. During the same visits, the flagged patients were interviewed by the study personnel. This included myself, with occasional help from the department research coordinator in case I was in the operating room. This was done to ensure that no potential patients were missed and to avoid having patients come back to the hospital specifically to be interviewed for the study.

During the initial patient encounter, the inclusion and exclusion criteria were checked. The study was explained to the patients including potential harms or benefits. Consent was obtained during the same session. At this stage, a file was opened for each patient and the randomizing center (the hospital pharmacy) was notified in order to provide the treatment medication (Amiodarone or Placebo) based on the pre-existing block randomization protocol as explained in the methods section (Section 5.3). At this time, the study drugs were picked up by myself and given to the patient. The medication bottle included enough pills to cover the required 10 days of treatment (5 days pre-operatively and

5 days post-operatively, in addition to extra 2 days of emergency supplies in case the surgery was delayed). Every effort was made to re-schedule the case within those 2 days. In case this was not possible the patient would have to restart all over again before the next proposed date of surgery. This was fortunately not encountered however. The pills were given to the patient during the same clinic visit. All patients were contacted 3 days pre-operatively to ensure that they started taking their pills and to ask about any possible side effects. On the day of surgery patients were met by myself in the pre-operative area in order to obtain their medication bottle for safe keeping so that it does not get misplaced in the operating room.

Post-operatively in the ICU, the bottle would be returned to the patient's bedside, and an order in the chart to resume the study medications would be written by myself. In case the patients were still not eating post-operatively and were still intubated in the ICU, then the pills were given to them via a naso-gastric tube.

Routine post-operative monitoring included 2 days of cardiac telemetry in all routine patients, however this was extended to 7 days in our study population to ensure that no asymptomatic arrhythmia episodes were missed. This continuous cardiac telemetry was utilized for 7 days after surgery, unless patients were discharged from the hospital prior to that. No patient was sent home before the 5^{th} post-operative day, which is the usual length of stay.

All rhythm strips were reviewed daily by myself. Our cardiac monitors stored the rhythms for up to 3 days for each patient ensuring that no arrhythmias were missed during the review. Blood work was collected on days 0, 1, 2, and 4 post-operatively.

A post-operative data sheet was used to document all the variables of interest such as rhythm status, episodes of AF, duration of AF, hemodynamic instability, as well as all the blood work values and any complications as per study protocol (Section 5.4). This was also performed by myself on a daily or bi-daily basis. All patients were seen and examined by myself to ensure that no study medication side effects were present. I was not however part of the clinical team taking care of any of the study patients. Any concerns regarding the well being of the patient or suspected drug side effects were communicated to the treating clinical team however. None of the nurses, physicians, or study personnel were aware of the group assignment of any of the patients. The study medications looked exactly the same (Amiodarone and placebo).

All collected data were entered into an excel spreadsheet document by myself. Statistical analysis was then performed using SAS 9.1 (SAS Institute Inc, Cary, NC) as described in the Methods section (Section 5.10).

7.0 Problems Encountered In The Conduct Of This Trial and Solutions:

Various problems and issues were foreseen and encountered in the conduct of this trial. Mechanisms to deal with such issues were devised a priori.

7.1 Patient recruitment: Approximately 400 valve procedures were performed at the lone recruiting center (The Ottawa Heart Institute). It was believed that the required sample size of 162 would have been achieved within 1 year even with capturing less than 50% of potential patients. This assumes full cooperation from the surgeons to inform their patients about the study in the pre-operative clinic. Given than this is difficult in a busy clinical practice, it was decided to flag all potential patients prior to clinic dates and arrange for a meeting between myself or an assistant and the patients in a manner that did not interfere with clinic time. Nonetheless, many patients were also being recruited into other studies and were ineligible to be included in other trials. This problem became more apparent after the commencement of the trial. The recruitment phase of the study was extended to 18 months in order to capture more patients. This however did not yield many more patients given the fact that I had left the country by that time to pursue a fellowship in the United States and had to rely on the division staff to help with recruitment. Only 5 patients were recruited in the extra 6 months time. The study had to be terminated in January of 2006.

7.2 Surgery cancellation: Given that this medication had to begin days prior to proposed date of surgery, only elective, non-emergency cases could be included. Surgery cancellation is a real issue given our limited health care resources. In addition, many emergency cases take priority over booked elective cases that result in re-scheduling of many elective procedures. Every effort was made to minimize the occurrence of such cancellation in the study patients.

In addition, extra drug capsules (extra 2 days supply) were included in each bottle to allow patients to continue taking their medications pre-operatively up to the new date of surgery. Every effort was also made to re-schedule these patients within 2 days of cancellation. This affected 3 patients, 2 were rescheduled within 2 days but one was not and was actually never re-enrolled again in the study.

7.3 Post-operative follow-up: This was divided into in-hospital and post-discharge follow-up. Study patients were followed very closely by myself to ensure that none of the outcomes or complications were missed. All patients were attached to continuous cardiac monitors for 5 days or until hospital discharge. These monitors record and store all rhythms for up to 48 hours. Therefore, in-hospital follow-up was felt to pose no problems to the study. Also, in order to minimize patient self-reporting bias post-discharge, all patients were contacted post-operatively in order to document any post-discharge AF or any complications that could be attributed to Amiodarone, AF or AF-related complications such as strokes or bleeding.

7.4 Hospital Staff Education: Medical and nursing staff involved in the care of the study patients were all educated about the existence of the trial, its objectives, intervention arms, and also mechanisms to address any problems in the conduct of the trial. This was felt to minimize the risk of forgetting to administer the study medications to patients and the close monitoring of any medication related side effects.

7.5 Inadequate Funding: The division of Cardiac Surgery agreed to assist financially in case the external fund was inadequate to complete the study. In addition further resources were also provided such as clinic time, office space and supplies in order to facilitate the conduct of the trial.

7.6 Patient Adherence and non-compliance: The study drugs (Amiodarone or Placebo) had to start 5 days prior to the proposed date of surgery. Many of the patients were screened and enrolled days or weeks prior to that date. Therefore, all patients were contacted pre-operatively to ensure that they started taking the drugs and to also inquire about any possible side effects. This was done 2 days after starting to take the study drugs.

7.7 Personal Reasons:

Effective and efficient patient recruitment suffered after I returned to clinical work, both in Ottawa, but especially after leaving the city. I moved to the United States for a year, then to London, Ontario in order to pursue more sub-specialized clinical training in my field. This made it more difficult to enroll patients into the trial. An average of 3-5 patients were enrolled into the study every month in the first 12 months while I was in Ottawa. This number unfortunately dropped to 4 patients only in 6 months after my departure. It as quite difficult to find the personnel to support the continuation of the study in my absence.

8.0 Results:

8.1 Patients:

A total of 114 patients were identified as meeting the inclusion criteria throughout the 18 months study period. Of these, 63 patients were excluded mainly due to medial reasons (Table 1), 2 patients declined to enroll and 2 patients were randomized but did not take any of their medications by their choice. These 2 patients were not followed post-operatively or included in the study. A total of 47 patients were randomized to either arm of the study, Amiodarone or Placebo and adhered to the study protocol. A total of 6 patients were withdrawn from the study during the trial. One was withdrawn pre-operatively after receiving 3 days of the study drug (Amiodarone) due to bradycardia. The remaining 5 were withdrawn post-operatively having received the total pre-operative loading dose for 5 days. Three of these patients were withdrawn due to post-operative complete heart block (bradycardia) requiring temporary pacemakers. This was done in compliance with the study protocol when the heart rate did not recover 2 days post-operatively (Section 5.7). None of these patients required permanent pacemakers however. Two of these patients had received Amiodarone and one received Placebo. The remaining 2 patients were withdrawn by their attending surgeons without clear reasons for such action. All these patients were included in the final analysis of the study given the conservative intention-to treat design of the study.

All patients enrolled in the study were enrolled due to valve heart surgery except for 2 CABG patients who were enrolled due to poor ventricular ejection fractions.

Patient inclusion based on older age alone was avoided in order to achieve the greatest possible number of valve patients in the study due to the clinical interest in such patients and in order to avoid a mainly CABG patient population similar to all previous

published studies. Given the slower than expected patient recruitment, the study was terminated prior to the inclusion of patients based on older age alone. Consequently the majority of patients in this study were valve patients (45 of 47).

Many patients were initially excluded based on prolonged QTc intervals (> 450 ms). This was a fairly conservative and strict requirement. This criterion was later amended to include patients with QTc intervals up to 500 ms given the fact that available evidence suggested that only QTc intervals greater than this threshold would be detrimental and could possibly lead to ventricular arrhythmias (64,65). Unfortunately no new patients with QTc > 500 were enrolled after the change of the policy and at the time of study termination. Adherence with the study medication schedules and protocols was 100%.

Table 2 displays the basic characteristics of patients in both groups. There were no clinically important or statistically significant differences between the Placebo and Amiodarone patients in all baseline demographics. None of the cases were urgent or emergent and none of the patients required pre- or post-operative intra-aortic balloon pump support. Only 3 procedures had to be re-scheduled in the Placebo group (12%) vs. none in the Amiodarone group. Patients continued to take their medications until the date of surgery since they had enough supplies in the medication bottle. No differences were found between the 2 groups in the utilization of pre-operative beta-blockers, calcium channel blockers, or Angiotensin converting enzyme inhibitors (ACEI). Of note however, less patients in the Amiodarone group had concomitant coronary artery bypass grafting during their valve surgery (9% vs. 28%) albeit this difference was not statistically significant given the small sample size.

8.2 Intra-operative Outcomes:

Table 3 displays the main intra-operative outcomes and events. More patients in the Amiodarone group (25%) required intra-operative inotropic support compared to the Placebo group (4%; P=0.04). There were no differences in duration of cardiopulmonary bypass time (pump time) or heart cross-clamp times however. No differences in adverse intra-operative outcomes such as death, hypotension, or arrhythmias were noted.

8.3 Clinical Outcomes:

Tables 4 and 5 display the main clinical outcomes, laboratory values and complications in both study groups.

8.3.1 Primary Outcome:

Clinically important post-operative AF occurred in 36.4% (95% CI 16.35% to 56.45%) of patients in the Amiodarone group compared to 40.0% in the Placebo group (95% CI 20.8% to 59.2%). This difference was not statistically significant (P=0.8, Table 4).

8.3.2 Secondary Outcomes:

Table 4 Displays the values of the secondary end-points.

- No differences in the rates of "any" post-operative AF were noted. The rates of *any* post-operative AF were actually the same as the "clinically-significant" post-operative AF episodes (the primary end-point) since all encountered post-operative AF episodes in this study population met the criteria for clinically significant AF as defined in this study (Section 5.4).

- The total duration of post-operative AF in patients who developed this condition was 940 minutes (± 1574 SD) in the Amiodarone group compared to 762 minutes (± 391

SD) in the placebo group. This difference did not reach statistical significance however with our small sample size (P= 0.8).

- The majority of patients were in normal sinus rhythm at the time of discharge from hospital (86% in the Amiodarone group vs. 96% in the Placebo group; P=0.22).

- None of the patients in either group sustained postoperative MI as defined in Section 5.4.

- No differences in mortality were noted between the two study groups. In fact none of the study patients died in-hospital or post-discharge (up to 6 weeks follow-up).

- None of the patients were in shock post-operatively or required intra-aortic balloon pumps.

- Table 4 shows that there were no statistically significant differences in the rates of AF-related complications between the two groups. This included strokes, other thromboembolic complications, or bleeding rates (secondary to anticoagulation). Only two patients sustained thromboembolic events. Both of these patients were in the Amiodarone group. One patient sustained post-operative AF (and had a stroke) while the other did not develop post-operative AF but sustained a transient ischemic attack anyways after going home which resolved. Of note the patient who had a stroke was the patient who was withdrawn from the study pre-operatively after taking the study medication for 3 days only prior to his procedure. In addition this patient was quite exceptional. He underwent a massive procedure to replace his aortic valve and ascending aorta including cooling the patient down to 18 ^{o}C and using hypothermic circulatory arrest due to the existence of a severely calcified aorta. This by itself dramatically increased his risk of stroke regardless of the onset of post-operative AF. This patient in fact had multiple severe co-morbidities

including peripheral vascular disease, renal failure, dialysis and also remained in the hospital for a prolonged period of time after his procedure (19 days at the Heart Institute including 8 days in the ICU) after which he was transferred to a rehabilitation center for unknown number of days.

As for bleeding complications, 8 out of 25 patients in the Placebo group (32%) received blood transfusion compared to 4 out of 22 in the Amiodarone group (18%, P=0.48). All such transfusions were actually administered early in the post-operative period, either in the operating room or in the ICU. This occurred prior to the institution of any anticoagulants and therefore was not related to either the occurrence of AF or study group allocation.

8.3.3 Electrolytes:

No differences in electrolyte or complete blood count values were noted between patients in the Amiodarone group vs. the Placebo group. Of importance potassium levels were comparable between the 2 study groups as measured on days 0,1, 2 and 4 post-operatively (Table 5). Also no differences in Glucose levels were noted.

8.3.4 Discharge Medications:

Table 6 displays the utilization of the different cardiac medications on discharge by patients in both groups. No differences were noted between the groups. Of note, a large number of patients in both groups were on beta-blockers at the time of discharge (80% vs. 59% in the Placebo and Amiodarone groups respectively). This difference is sizeable despite the fact that the "P" value was not significant given the small sample size. The utilization of beta-blockers pre-operatively was almost the same in both groups (20% vs. 18%). Almost all the

patients in both groups were discharged home on Aspirin. Post-operative aspirin is routinely used after either coronary bypass surgery or valve operations.

8.4 Economic Analysis:

A cost analysis was performed in this study. No cost-effectiveness or cost-benefit analysis was performed given the fact that there were no differences in primary or secondary outcomes to use in the "difference in effect" side of the equation. Capital and procedure-related costs between the groups were not documented given that fact that they were the same regardless of treatment group allocation. The main differences in cost were related to differences in length of hospital stay (including ICU days), the need for blood transfusions and the actual study drugs. The cost of treating AF related complication such as the need for grastroscopy for gastrointestinal bleeding would have been relevant and had to also be included in the cost analysis of the patients who might have had such procedure. This was not the case in any of the study patients however. No serious side effects were noted and no extra procedures were performed. Consequently, differences in hospital and ICU length of stay, blood transfusions, and the cost of Amiodarone accounted for most of the cost differences between the study groups.

8.4.1 Length of ICU stay:

The average length of ICU stay in the Placebo group was slightly less than the Amiodarone group (1.33 vs 1.95 days) (Table 5). This was not statistically significant however (P= 0.13). The cost per ICU day is approximately $2500 (66). Using SAS 9.1, the average cost of ICU stay per patient in the Placebo group was $3333.33±1209.9 compared to $4880.95±4774.7 in the Amiodarone group (P=0.13). This indicates that the ICU cost per patient was actually greater in the Amiodarone group compared to the Placebo group by an average of $1547.62 (4880.95-3333.33).

8.4.2 Ward and Overall hospital length of stay:

No difference in the overall length of hospital stay between the 2 groups was noted (7.64 days vs. 7.81 days in the Placebo and Amiodarone groups respectively; P=0.93). This included total time spent in the hospital (ICU and the wards). The cost of hospitalization therefore was made up of both ICU and ward costs. The cost per day on the regular ward was approximately $750 compared to $2500 in the ICU (66). The average number of days spent on the ward in the Placebo group was (7.64 - 1.33 = 6.31 days) compared to 5.86 days in the Amiodarone group (7.81 - 1.95). The average cost of days spent on the ward per patient was $4812.5±4095.5 in the Placebo group compared to $4392.86±4407.1 in the Amiodarone group (P=0.74). Table 7 summarizes the costs of hospitalization (ICU, wards, and total hospitalization).

8.4.3 Number of patients receiving blood transfusions:

Many patients required blood transfusion either in the operating room or shortly thereafter (32% in the Placebo group vs. 18% in the Amiodarone group). The number of units given per transfused patient was 1 unit. It was not clear why the rates of transfusions where greater

in the Placebo group. While this difference was not likely to be related to treatment group assignment, this difference was accounted for and entered into the cost analysis. The cost per unit of blood is approximately $300 (67). A total of 8 units of blood were transfused to 8 patients in the Placebo group (total of $2400) compared to a total of 4 units of units transfused to 4 patients in the Amiodarone group (total of $1200). Of note the Placebo group included 3 more patients overall. This translates into an average cost of blood transfusion of $ 96 per patient in the Placebo group (2400/25 = 96) vs. $ 54 (1200/22=54) in the Amiodarone group (difference $42, P=0.29, Table 7).

8.4.4 Cost of Amiodarone:

The cost of the generic oral form of Amiodarone has depreciated in price. A 10-day course of this medication would cost approximately $ 75 per patient in an outpatient regular pharmacy.

8.4.5 Overall average difference in cost per patient:

Table 8 displays the average cost per patient in the Amiodarone and Placebo groups. The average cost per patient was $ 1078.87 greater in the Amiodarone group (9355.95-8277.08) without a clinically important difference in the primary outcome (3.6% reduction in the incidence of AF with no difference in complication rates). This would lead to the conclusion that Amiodarone was not cost effective in this setting as it is associated with higher cost with no identifiable benefits. Based on the cost difference within the trial of $1078.87 and the difference in the primary outcome of 3.6% reduction in AF (40% - 36.4%); the cost per AF episode avoided would be $29,968.61 (1078.87/0.036).

9.0 Discussion:

This study focused on utilizing a prophylactic agent to reduce the incidence of post-operative AF in a very selective group of cardiac surgery patients. The focus of the trial was initially intended to include valve patients, the elderly (age >70), and patients with poor ventricular function (Ejection fraction < 40). The incidence of post-operative AF is known to be greater in these patients based on previous reports (7,8,9).

Valve patients made up the majority of the study population due to the limited number of patients with poor left ventricular ejection fractions (LVEFs). Only 2 patients were enrolled due to poor LVEFs and no patients were enrolled due to being above the age 70 alone. A single surgeon whose practice included mainly valve patients contributed the most to the study population. This skewed the study population to include valve patients almost exclusively (90% of patients). Furthermore, initially patient recruitment focused mostly on enrolling valve patients in order to avoid having mostly CABG patients in this study. This patient population already made up the majority of patients in the previous published studies. This was unfortunate in a way since the study was terminated before enough non-valve patients were recruited. Therefore, the results of this study could only be generalized to valve patients. It could be argued that had we enrolled valve patients only initially and CABG patients (elderly and poor LV function) added later, a temporal bias might have been introduced. This was not an issue in this study since only 2 patients out of 47 were non-valve patients. In addition, no major changes in treatment modalities over the study period occurred that could affect any clinically significant outcomes. Despite this weakness, this study remains one of 2 studies that examined the effects of utilizing

Amiodarone as a prophylactic agent to reduce post-operative AF in valve surgery patients alone, the other being the PABABEAR trial (57). It is important therefore to interpret the outcomes of the study in light of the fact that they only apply to valve patients and no real comments could be made regarding the influence of Amiodarone on AF rates in the elderly or in patients with poor heart ventricular functions. It follows that results of this trial could only be applied to valve patients.

The internal validity of this study was acceptable, albeit not perfect given the small sample size. All patients were allocated to the treatment groups in a randomized, blinded fashion to minimize differences in known and unknown potential confounding variables. Neither patients nor study personnel had any control or knowledge of the groups that patients were assigned to. The differences in the underlying basic patient characteristics were similar between the study groups. In addition, none of the study personnel was involved in the clinical care of any of the study patients. This was done in order to minimize any prior biases that the study personnel might have in addition to making the study more generalizable by allowing study patients to be treated similar to all other patients except for receiving the study tablets. Furthermore, both Amiodarone and Placebo capsules were identical in appearance and no differences in taste existed either. The results of the study however could only be applied to a similar patient population. Specifically the outcomes of this trial can only be generalized to cardiac patients undergoing elective valve surgery and possess similar baseline characteristics to this study population.

The results of the trial were unexpected. The difference in the incidence of post-operative AF between the Amiodarone and Placebo groups amounted to a mere 3.6%, which was neither statistically or clinically significant. Only a third of the required sample size was achieved, yet it was clear that not even a real trend towards a clinical difference between the groups was apparent. This in fact is the only Amiodarone study that did not demonstrate any beneficial effects of Amiodarone in reducing the rates of post-operative AF (2,50-59). It was initially believed that if Amiodarone reduces post-operative AF in coronary bypass patients then more benefit would be expected in valve patients given the fact that AF is more common in that patient population. The negative outcome of the current study was initially very surprising yet a biologic explanation is plausible. Unlike coronary artery procedures on the surface of the heart, heart valve surgery involves cutting into cardiac structures which lead to more tissue irritation resulting in a greater incidence of post-operative arrhythmias such as AF. Consequently, it could be argued that given the structural damage to heart tissues then these patients would be more resistant to drug agents that attempt to reduce arrhythmias post-operatively. It is conceivable that the tissue damage created in the operating room, in addition to the secondary tissue inflammation, renders Amiodarone less effective in preventing the development of cardiac arrhythmias such as AF post-operatively. It could also be argued however that the reason for the negative study might not be the actual procedure performed or the agent Amiodarone itself, rather the loading dose could have been inadequate. While this could be a valid argument, however previous studies that demonstrated the beneficial effects of Amiodarone in reducing AF in CABG patients, used similar loading doses pre-operatively (2,57). This trial's findings are contrary to the findings of all previous conducted studies in this field (2,50-57,59). Furthermore, a greater proportion

of patients were discharged home in normal sinus rhythm in the Placebo group compared to the Amiodarone group. In addition, Placebo group patients who developed post-operative AF remained in this abnormal rhythm status for a shorter period of time compared to their Amiodarone counterparts. This was both not expected and contrary to previous published findings (2,57). For instance Daoud et al (2), demonstrated that Amiodarone-treated cardiac surgery patient not only had a lower incidence of post-operative AF (25% vs. 53%) but also remained in AF for a shorter period of time compared to their placebo-treated counterparts.

No differences in hard end points such as mortality were noted. This was not unexpected given the fact that AF-related mortality is a very uncommon. None of our study patients died in hospital or during the follow-up period at home (up to 6 weeks). The risk of death associated with cardiac surgery has decreased dramatically over the past 2 decades due to improved surgical techniques and post-operative medical care especially improved care in intensive care units. Furthermore, various other factors accounted for this expected result. Patients in this study were all elective low risk patients. It is a well-known fact that urgent or emergent procedures increase the risk of peri-operative mortality in addition to non-fatal complications such as myocardial infarction, strokes, infections and renal failure (68-71). All of our patients had to be elective patients in order to allow for a period of drug loading pre-operatively. In addition, the average age of our patients was also lower compared to the average cardiac surgery patient (61 and 57 years in the Placebo and Amiodarone groups in this study respectively vs. 65-70 years of age in average cardiac surgery patients).

No serious complications such as strokes or bleeding were encountered in any of our patients. This was both reassuring and satisfying. Only one patient had a transient ischemic attack post-operatively at home. The risk of stroke in the patient population is directly related to increased age and it increases substantially from 1% in younger patients to 10-15% in patients older than 80 years of age (71-73). A prior history of strokes or the presence of peripheral vascular disease is also believed to increase the risk of such events. Our patients were generally younger and none had a history of either stroke or peripheral vascular disease. This would certainly explain the low risk of complications in this study. The absence of serious side effects in patients using Amiodarone, especially in the pre-operative period was also very reassuring.

Generally, many patients who develop post-operative AF remain in AF for days. This usually necessitates the institution of anticoagulation with either heparin or coumadin, barring any contra-indications to such therapy. This is done to reduce the risk of thrombus formation in the left atrium that could lead to thromboembolic complications such as strokes, ischemic limbs or visceral organs (10,11,15). The risk of such embolic complications is believed to drop from 5% per year to 2% per year with the addition of anticoagulation. Anticoagulation however could delay hospital discharge and also increases the risk of hemorrhagic complications. None of our patients suffered a major hemorrhagic complication. None of the patients were transfused beyond the first post-operative day either. Few patients were transfused either in the operating room or in the intensive care unit due to intra-operative related events such as per-operative bleeding, anemia, or hemodynamic instability. None of these patients was anti-coagulated yet, and Amiodarone

assignment was not relevant or even related to such events since Amiodarone itself has no effect on bleeding. Furthermore, most surgeons institute anticoagulation for all valve patients for a period of 3 months after such procedures at any rate. This is done to reduce the risk of valve thrombosis given the initial raw surface of such valves. Therefore, it could be argued that the presence or absence of AF would be irrelevant if all valve patients had to be anticoagulated at any rate. This would mean that even if the rates of AF episodes were reduced with a certain agent, such as Amiodarone, these patients would still be exposed to the bleeding risk of anticoagulation. At any rate, both the incidence of AF and the use of anticoagulants were similar between the Amiodarone and Placebo groups in our study.

Many factors are believed to play a role in the development of AF (74-81). Electrolyte disturbances, especially potassium blood levels could increase the risk of AF. Other factors such as myocardial ischemia, anemia, the use of beta-blockers and other negative chronotropic agents, could also affect the occurrence of this arrhythmia. All of these variables were measured and compared in order to ensure that there were no differences between the groups at different points in time. Any differences could potentially affect the rates of AF among the study groups. The current study demonstrated no such differences in electrolyte or other laboratory values between the Placebo and Amiodarone groups that could contaminate and skew the results. Furthermore, no differences in myocardial infarctions were apparent between the groups, although this does not exclude the existence of less serious and silent myocardial ischemia that could potentially affect the rates of AF in this patient population. Other non-measured variables such as atrial stretch due to intravascular volume overload could also increase the chance of AF. This variable however

was difficult to measure outside the immediate post-operative period in the ICU using a central venous pressure (CVP) transducer. This measurement would be useless however given the fact that most AF episodes occur after the second or third post-operative day and no CVP measurements are available at that time given the fact that most patients would be on the ward by that time without any invasive monitors.

Given the fact that many cardiac medications could also control or reduce the incidence of AF, all those potential confounders had to be measured and accounted for in the study. Fortunately, no differences in the utilization of cardiac medications such as beta-blockers or calcium channel blockers were found pre-operatively. This reduced the risk of contaminating the results of the trial.

No differences in intra-operative complications or arrhythmias were found between the study groups. The occurrence of arrhythmias, hypotension and cardiopulmonary (heart-lung) bypass times were similar between the groups. The only exception was the need for more inotropic support in the Amiodarone group to help the failing heart come off the cardiopulmonary bypass machine. It is not clear why this was the case since Amiodarone by itself is not believed to decrease cardiac function per se. This could be a random statistical finding however given the fact that no biologic plausible explanation could be found. All these inotropic agents however were weaned off within 24 hours with no detrimental outcomes in any of the patients.

Peri-operative bradycardia was a concern in patients receiving Amiodarone given the negative chronotropic properties of this agent (slowing the heart rate). A total of 5 out of 22 (23%) patients required temporary pacing post-operatively in the Amiodarone group compared to only 3 out of 25 patients (12%) in the Placebo group. This difference was not statistically significant given the small sample size, however it was clinically important to note. A total of 3 patients were withdrawn from the study post-operatively due to bradycardia and their study medications terminated. All these patients required temporary pacemakers and belonged to the Amiodarone group. The need for pacemakers was fortunately transient and none of the patients required more aggressive therapy such as permanent pacemaker insertions. Nonetheless, this side effect of Amiodarone should be kept in mind by clinicians planning to use this agent prophylactically in the peri-operative setting. Beta-blocker utilization increased in the post-operative period in both groups, 80% in the Placebo group and 59% in the Amiodarone group. This difference was statistically insignificant given the small sample size. However, pre-operative beta-blockers were only used in 20% and 18% of Placebo and Amiodarone patients respectively. Cardiac surgery patients are routinely discharged home on beta-blockers in order to reduce post-operative tachycardia and reduce the risk of conversion to AF. It is possible that heart rates were more controlled in the Amiodarone group compared to the Placebo group leading to the decreased need to beta-blocker utilization post-operatively. No documentation of heart rates throughout hospitalization was available however to prove this hypothesis.

No statistically significant differences were noted in the overall length of hospital stay between the two groups, although any trend would be for greater length of stay in the

Amiodarone arm. The patients had similar baseline characteristics and also underwent similar procedures (valves). It was initially hypothesized that reducing AF rates would lead to reduced hospital days given the fact that the onset of AF would have necessitated anticoagulation prior to hospital discharge in many patients. This would have led to an increase in the number of hospital days by an average of 2 days in the Placebo group. However all surgeons anticoagulated all valve patients routinely for at least 3 months after surgery which rendered this initial hypothesis inaccurate.

The cost of surgery and the use of hospital infrastructure were the same between the two study groups. Most differences in economic costs were believed to occur as a result of possible differences in hospital or ICU length of stay or due to the cost of treating post-operative AF or the treatment of AF-related complications such as bleeding or strokes. Many of these complications invariably lead to increased economic costs mainly due to increased hospital length of stay. Given that the differences in outcomes (benefit or harm of Amiodarone) were not considered clinically important, the cost-analysis part of the equation became the main economic outcome of the study. This analysis looked at the differences in cost between the groups (Delta cost) since a cost-effectiveness or cost-benefit analysis would not be of any value required given the similar denominator (difference in outcome between the groups of only 3.6%). The overall difference in cost between the 2 groups amounted to a mere average of $1078 per patient. This is very small compared to the overall cost of surgery and hospitalization of these patients (approximately $20,000 for each patient). It was interesting to note however that the cost was greater in the Amiodarone group compared to the Placebo group despite the fact that the cost of the medication would

have only accounted for $75 per patient. Despite this, a brief cost-effectiveness analysis was performed in order to evaluate the added cost needed to save one AF episode using a difference of 3.6% in the primary outcome. This amounted to approximately $30,000 added cost per episode of AF saved. Given the fact that there was no cost saving attributed to the use of Amiodarone and the fact that the clinical benefits were so negligible, it would be quite difficult to recommend using this agent in this patient population. If the difference was accepted as clinically important however, a decision maker would need to value an AF episode avoided as being worth approximately $30,000 for Amiodarone to be considered cost effective. Almost all Amiodarone trials failed to demonstrate any economic benefits to such prophylactic therapy except for 1 study (2).

A variety of obstacles had to be overcome in the conduct of this trial. Patient recruitment into the study was the most challenging part of the trial. Only 30% of the intended sample size was recruited into the study after 18 months of recruitment. A variety of obstacles contributed to such failure to achieve the required sample size. As noted in the results section, a large number of patients were excluded based on contra-indications to Amiodarone use. May patients were bradycardic to begin with given the wide-scale use of beta-receptor blocking agents. Amiodarone also slows down the heart, and no patients with heart rate < 60 beats per minute were included in the trial as a result. In addition, many patients had prolonged QTc intervals which also led to the exclusion of many potential study candidates. Another issue was the poor referral into the study by some of the clinicians. In order to minimize this, most patients were screened prior to being assigned to surgeons and then approached in clinics. Despite all this patient recruitment remained lower than

expected. Many patients were operated soon after being assed by the surgeons and therefore they did not have the necessary 5 pre-operative days to begin the study medications. Another common problem was the fact that many patients had to be enrolled in other studies and could not be enrolled in more than one trial concomitantly. This problem became more apparent after commencing the trial. Furthermore, the majority of patient recruitment into the study was performed by myself, with some assistance form the division research nurse. All patients had to be contacted 2 days after starting the medication at home in order to ensure that no side effects necessitating medical attention were present. Recruitment became very difficult after returning to resume my clinical training in addition to the unexpected departure of the division research nurse who aided in patient recruitment. This problem was compounded by my departure to the United States in 2005 to pursue further sub-specialized surgical training. This, as expected, severely compromised my ability to recruit and follow patients. Only 5 patients were recruited over the last 6 months of the study while I was in the United States compared to about 4 to 5 patient recruitments per month when I was physically present in Ottawa. Given the time limitation to end the study, financial constrains and my departure. The study was stopped in January of 2006, which allowed for 18 months of recruitment.

The assistance of the randomizing center (the hospital pharmacy) was ensured and was extremely helpful. A single pharmacist performed the randomization of all patients using a pre-printed block-randomization sequence that was not available to any of the study personnel. The pharmacist was fully informed of the goals and protocol of the study and had agreed to assist me in this endeavor. Records of all patients and their allocation assignments

to either the study or placebo groups were kept completely confidential and stored in the hospital pharmacy. Study personnel had no access to such records until the end of the study. This ensured that the study was conducted in a strict double-blinded fashion.

All patients except for two, were very cooperative and initiated the study medication pre-operatively according to protocol. No adherence issues were encountered in the remaining 47 included patients. This aspect of the study conduct was very satisfying.

Given the negative results of this study, it would be difficult to recommend routine peri-operative use of the anti-arrhythmic agent Amiodarone to reduce the incidence of post-operative AF. It could be argued however that this study lacks the necessary power to make such statement. While this is always a strong argument in negative outcome trials, the fact that there was not a real trend towards a difference between the treatment groups lends support to this trial's negative conclusion despite the lack of statistical power.

This was the only trial that demonstrated lack of benefit of Amiodarone in preventing post-operative AF in cardiac surgery patients. However, this has to be seen in light of the fact that the majority of patients in previous trials were CABG patients. In fact, most studies have focused on CABG patients exclusively, whereas 2 studies included valve patients in addition to CABG patients (2,57). These studies demonstrated that Amiodarone did reduce post-operative AF in valve patients based on post-hoc subgroup analyses. This type of post-hoc analysis is quite problematic and is fraught with weaknesses. This is due to the fact that valve patients in these studies were not randomly assigned to receive either

placebo or Amiodarone. This could potentially weaken the internal validity of such analyses due to imbalances in known and especially unknown baseline characteristics and confounders rendering the results either invalid or at the very least questionable.

In conclusion, no clinical or economic benefits were demonstrated with the use of Amiodarone to reduce per-operative AF in patients undergoing heart valve surgery. In addition, an increase in bradycardia episodes, albeit transient, was noted. The required study power was not achieved however. Only a third of the required sample size was achieved at the end of the recruitment phase of the study. The conduct of this trial was extremely challenging due to a variety of foreseen and unforeseen reasons. The actual process of securing funding, educating the clinical staff, obtaining ethics approval, patient recruitment, study conduct, collection and analysis of the results in addition to many organizational and patient related obstacles and issues provided me with a very enriching but humbling experience.

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Figure 1. PAPABEAR trial design:

Flow of Patients Through the PAPABEAR Trial

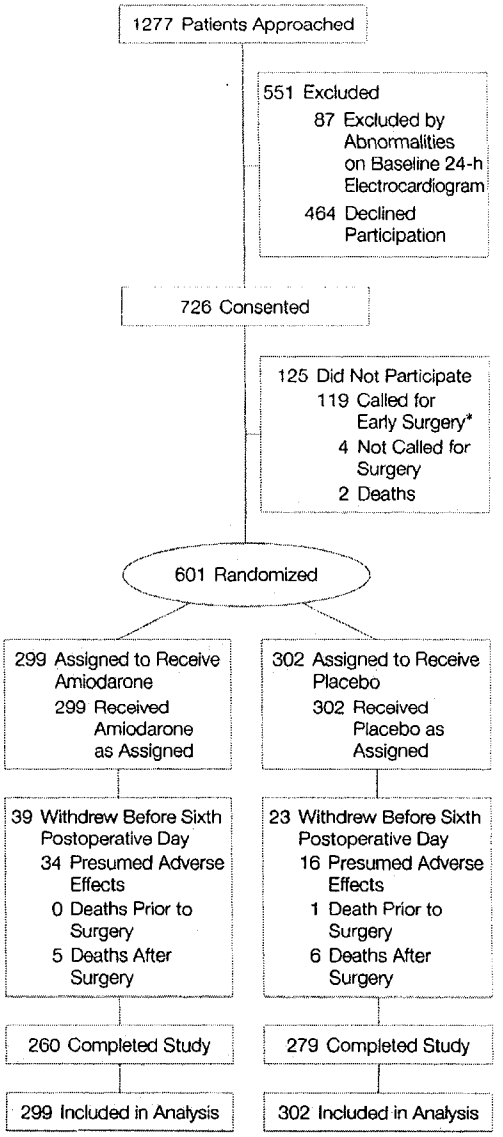


Figure 2. Experimental Time-line.

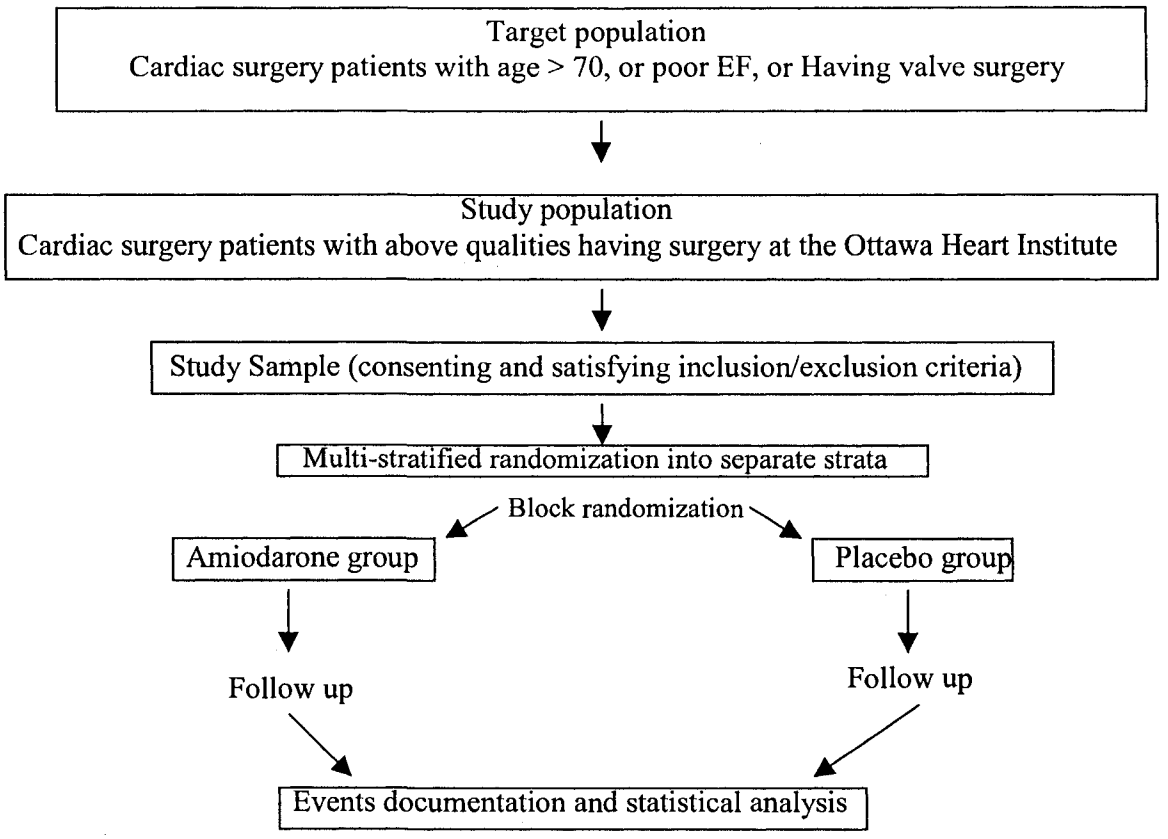


Table 1. Excluded Patients During Screening.

	Reason for Failure
1	Lung dx
2	Qtc>450
3	refused
4	refused
5	Bradycardia
6	Refused
7	No surgery (medical decision)
8	Bradycardia
9	decided No surgery
10	Afib and Qtc 464
11	pt refused
12	legal issues
13	BBBlock
14	Breast ca
15	Afib
16	Unknown
17	Bradycardia
18	Unknown
19	Bradycardia
20	Bradycardia
21	Bradycardia
22	Missed Clinic
23	QTC>450
24	declined
25	QTC 490
26	HR 47
27	QTC>450
28	Qtc >450, & Hypothyroidism
29	Cardiotomy Trial
30	COPD
31	Cardiotomy Trial
32	surgery reschedule
33	SOA
34	Unkown
35	Unknown
36	Bradycardia
37	Missed
38	cardiotomy
39	Cabg and >70yo
40	Cardiotomy Trial
41	afib status
42	QTC > 450
43	Bradycardia
44	QTC > 450

45	QTC > 450
46	paced
47	afib status
48	afib status
49	HR 50
50	afib status
51	no incluslon criteria
52	QTC > 450
53	afib status
54	QTC > 450
55	QTC > 450
56	QTC > 450/post consenting
57	afib status
58	afib status
59	1 degree heart block
60	Patient changed mind
61	cardiotomy
62	± Maze Precudure
63	1 degree heart block found post consenting

Table 2. Basic patient Characteristics, (Mean± SD for continuous variables).

N= 47	Placebo (N=25)	Amiodarone (N=22)	"P" Value
Age (years)	61.68±13.04	57.73±12.24	0.29
Sex (male)	16/25 (64.0%)	16/22 (48.48%)	0.41
Height (m)	1.69±0.08	1.69±0.09	0.92
Weight (kg)	81.04±14.53	74.99±13.66	0.16
BMI	28.31±4.53	26.34±4.52	0.15
BSA (m2)	1.92±0.20	1.86±0.21	0.35
Obesity (Yes)	9/25 (36.0%)	6/21 (28.71%)	0.59
CAD/CABG	7/25 (28%)	2/22 (9%)	0.1
Pre-op MI	2/25 (8%)	1/22 (5%)	0.63
Pre-op DM	1/25 (4%)	1/22 (5%)	0.37
Pre-op HTN	12/25 (48%)	7/22 (32%)	0.26
Pre-op Cholesterol	10/25 (40%)	6/22 (27%)	0.42
Pre-op AF	3/25 (12%)	1/22 (5%)	0.36
Pre-op PVD	0/25 (0%)	1/22 (5%)	0.28
Pre-op CRF	0/25 (0%)	1/22 (5%)	0.28
Pre-op TIA	1/25 (4%)	2/22 (9%)	0.48
Pre-op CVA	0/25 (0%)	0/22 (0%)	NA
Pre-op COPD	3/25 (12%)	0/22 (0%)	0.09
Pre-op Liver Disease	0/25 (0%)	0/22 (0%)	NA
Pre-op LV Class I	19/24 (79%)	13/17 (76%)	0.93
Pre-op LV Class II	3/24 (13%)	2/17 (12%)	
Pre-op LV Class III	2/24 (8%)	2/17 (12%)	
Pre-op BB	5/25 (20%)	4/22 (18%)	0.87
Pre-op CaB	4/25 (16%)	0/22 (0%)	**0.05**
Pre-op ACEI	8/25 (32%)	13/22 (59%)	0.06
Pre-ASA	9/25 (36%)	8/22 (36%)	0.98
Pre-Plavix	1/25 (4%)	1/22 (5%)	0.93
Pre-Coumadin	2/25 (8%)	1/22 (5%)	0.63
Pre-op Diuretics	8/25 (32%)	10/22 (45%)	0.34
Pre-op Statins	10/25 (40%)	5/22 (23%)	0.21
Pre-op NSR	25/25 (100%)	22/22 (100%)	NA
Pre-op HR	69.6±9.28	69.32±11.95	0.93
Pre-CI	2.1±0.36	2.1±0.24	0.76
Pre-op Hgb	139.39±18.28	137.61±20.67	0.77
Pre-op K	4.07±0.43	4.08±0.43	0.44
Pre-op Creat	80.32±13.04	88.16±21.89	0.16
Pre-op Gluc	5.95±1.45	5.78±1.92	0.76
OR Cancellation	3/25 (12%)	0/22 (0%)	0.1
Pre-op Adverse Events	0/25 (0%)	1/22 (4%)	0.27

BMI: Body mass index; BSA: Body surface area; CAD: Coronary artery disease; CABG: Coronary artery bypass grafting; MI: Myocardial infarction; DM: Diabetes Mellitus; HTN: Hypertension; AF: Atrial fibrillation; PVD: Peripheral vascular disease; CRF: Chronic renal failure; TIA: Transient ischemic attack; CVA: Cerebrovascular accident; COPD: Chronic obstructive pulmonary disease; LV: Left ventricle; BB: Beta blockers; CaB: Calcium blockers; ACEI: Ace inhibitors; ASA: Aspirin; NSR: Normal sinus rhythm; HR: Heart rate; IABP: Intra-aortic balloon pump; CI: Cardiac index; Hgb: Hemoglobin; K: Postassium; Creat: Creatinine; Gluc: Glucose.

Table 3. Intra-operative Data, (Mean± SD for continuous variables).

N= 47	Placebo (N=25)	Amiodarone (N=22)	"P" Value
CPB (min)	100.44±32.4	105.81±31.83	0.58
X-Clamp (min)	71.13±26.54	73.40±17.33	0.74
Intra-op Inotrops	1/25 (4%)	5/20 (25%)	0.07
Intra-op VT	1/25 (4%)	3/21 (14%)	0.3
Intra-op AF	1/24 (4%)	1/21 (5%)	0.4
Intra-op Bradycardia	1/24 (4%)	1/21 (5%)	0.4
Intra-op Shock	0/18 (0%)	2/17 (12%)	0.08
Blood Transfusion	8/25 (32%)	4/21 (19%)	0.48

X-clamp: Cross clamp time; VT: Ventricular tachycardia; AF: Atrial fibrillation

Table 4. Post-operative complications, (Mean± SD for continuous variables).

N= 47	Placebo (N=25)	95% CI	Amiodarone (N=22)	95% CI	"P" Value
AF (%)	10/25 (40%)	20.8% to 59.2%	7/22 (36.4%)	20.8% to 56.5%	NS
Total AF Duration (min)	762 ± 391	608.7 to 915.3	940 ± 1574	282.3 to 1597.7	NS
CVA/TIA	0/25 (0%)	0	2/22 (9%)	-3% to 21%	NS
Bleeding	8/25 (32%)	22.7% to 41.3%	4/22 (18%)	2% to 34%	NS
Re-opening for Bleeding	4/25 (16%)	1.6% to 30.4%	1/22 (5%)	-4.1% to 14.1%	NS

AF: Atrial Fibrillation; CVA: Cerebrovascular Accident (stroke); TIA: Transient Ischemic Attack; NS: Not Significant; NA: Not applicable; CI: Confidence Interval; P value of ≤ 0.05 is considered significant.

Table 5. Post-operative Data, (Mean± SD for continuous variables).

N= 47	Placebo (N=25)	Amiodarone (N=22)	"P" Value
Re-opening in ICU	4/25 (16%)	1/22 (5%)	0.22
Blood Transfusion	8/25 (32%)	4/22 (18%)	0.48
Post-op K day 0	4.15±0.36	4.11±0.36	0.68
Post-op K day 1	4.28±0.39	4.34±0.31	0.55
Post-op K day 2	4.08±0.38	4.05±0.35	0.75
Post-op K day 4	3.74±0.62	3.94±0.54	0.27
Hospital LOS	7.64±5.44	7.81±6.68	0.93
ICU LOS	1.33±0.48	1.95±1.9	0.13
Post-op Pacing	3/25 (12%)	5/22 (23%)	0.32
Discharge Rhythm (NSR)	24/25 (96%)	18/21 (86%)	0.22

SD: Standard Deviation; ICU: Intensive care unit; CI: Cardiac index; Hgb: Hemoglobin; K: Potassium; Creat: Creatinine; Gluc: Glucose; IABP: Intra-aortic balloon pump; LOS: Length of stay; NSR: Normal Sinus Rhythm.

Table 6. Discharge Cardiac Medications.

N= 47	Placebo (N=25)	Amiodarone (N=22)	"P" Value
Beta Blockers	20/25 (80%)	13/22 (59%)	0.29
Ca Blockers	6/25 (24%)	1/22 (5%)	0.08
ACE / AII Inhibitors	11/25 (44%)	11/22 (50%)	0.57
Amiodarone	0/25 (0%)	2/22 (9%)	0.11
Digoxin	2/25 (8%)	1/22 (5%)	0.66
Diuretics	9/25 (36%)	7/22 (32%)	0.85
ASA	25/25 (100%)	20/22 (91%)	0.27
Coumadin	16/25 (64%)	10/22 (45%)	0.26

Table 7. Average cost *per patient* in both the Placebo and Amiodarone groups (average ICU cost *per* patient, average ward cost per patient, medication cost per patient, average transfusion cost per patient, and average overall cost per patient). ***This excludes common costs such as the surgical procedure and medical and nursing fees.***
(Mean ($)± SD for continuous variables).

	Placebo	**Amiodarone**	**P**
ICU Cost *per* patient	3333.33±1209.9	4880.95±4774.7	0.13
Ward Cost *per* patient	4812.5±4095.5	4392.8±4407.1	0.74
Medication Cost *per* patient	0	75	NA
Transfusion Cost *per* patient	96±142.8	54.5±118.4	0.29
TOTAL Cost *Per* Patient	$ 8277.08±4417.9	$ 9355.95±7446.8	**0.55**

SD: Standard Deviation; ICU: Intensive Care Unit.

Appendix A: Amiodarone Side Effects.

- Bradycardia (Slow Heart Rate)

- Heart Blocks (Leading to Bradycardia and Hypotension)

- Hypotension

- Prolonged QTc leading to ventricular arrhythmia (Torsade de Pointe)

- Interstitial Lung Disease & Fibrosis

- Hypothyroidism

- Liver Toxicity

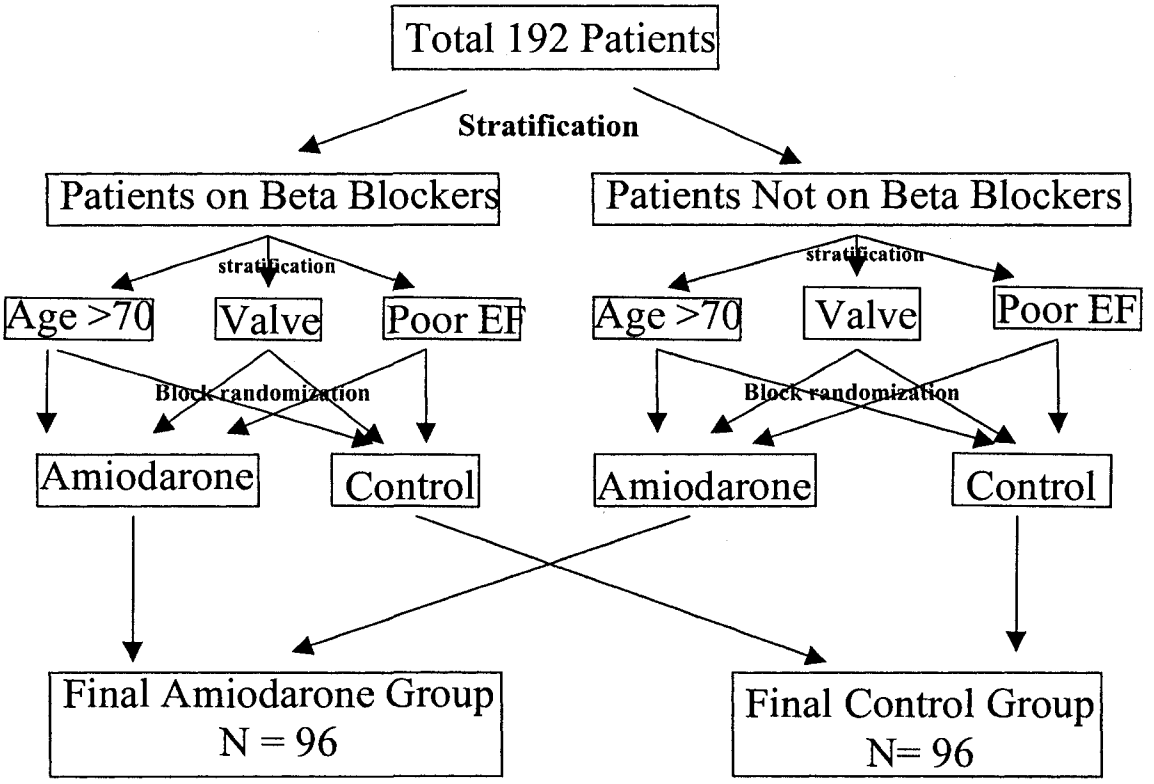
- Anaphylaxis

- GI Upset

Appendix B: Inclusion and exclusion criteria of the study population.

Inclusion criteria:	***Reason:***
- Elective cardiac surgery patients at high risk of post operative AF (valve or combined valve and CABG patients, or age ≥ 70 years, or patients with poor left ventricular ejection fraction $\leq 40\%$)	- The population of clinical interest
- Normal Sinus Rhythm	
- Consenting	
Exclusion criteria:	***Reason:***
- Resting heart rate < 60 beats per minute	- To avoid bradycardia
- Systolic blood pressure (SBP) < 100 mmHg	- Potential slight decrease in SBP with amiodarone
- Long QTc interval (>500 ms) on baseline electrocardiogram	- Small risk of increased QTc interval and ventricular arrhythmias
- History of interstitial lung disease (ILD)	- Rare cases of ILD with amiodarone
- known allergy to amiodarone	- Contraindication for drug use.
- History of thyroid disease	- Potential for hypothyroidism
- History of amiodarone use within last 2 months of the trial	- To ensure drug washout
- Patients with second or third degree heart blocks	- Due to small risk of worsening heart blocks
- Current use of class I or III anti-arrhythmic medications (example procainiamide or sotalol)	- To avoid drug interactions and potential arrhythmias
- Patients on two chronotropic agents (such as combined digoxin and beta blockers, or combined calcium blockers and beta blockers)	- To avoid bradycardia
- Chronic continuous atrial fibrillation	- Unlikely to benefit from this treatment
- Patients undergoing AF ablation	- Would confound the results.

Appendix C: The Multi-Stratified Randomization Process showing the steps of stratification and block randomization and the required number of study patients to achieve the full study power (+ 15% extra to account for losses to follow-ups):



In the actual trial, only 47 patients were recruited as follows:

45 had valve surgery (7 on pre-operative beta blockers, 38 not on beta blockers).

2 had CABG but enrolled for poor ejection fractions (both on beta blockers).

No patients were recruited due to older age alone.

Appendix D: A total of 6 study strata were created in this trial. Patients were either on pre-operative beta blockers or not; then within each of these 2 groups, 3 sub-strata were created: Valve patients, age > 70 years, and poor ejection fraction (< 40%).

Random, computer generated sequences of 4 and 6 treatment blocks were used to assign patients to either the Amiodarone or the Placebo groups within each of the 6 study strata. Separate sequences were used for each of the study strata. An example of one such random sequence would be:

AACC ACACAC CACA CCAACA ...etc (for each of the strata, example valve patients on beta blockers stratum)

Where (A) is Amiodarone treatment and (C) is control.

Each newly recruited patient was allocated to the next randomized treatment assignment by a central unit (pharmacy) in order to maintain the blinding of patients and study personnel. Patients were given their drug bottles that had a unique identifying number that can be linked to drug assignment at the end of the study by the central unit to the treatment received (either Amiodarone or Placebo).

Appendix E: Protocol for initiation of AF treatment.

1) Unstable AF (Symptoms such as shortness of breath, weakness, lightheadedness, or decreased systolic blood pressure to < 100 mmHg)

2) Stable AF with heart rate 100 – 120 beats per minute for > 5 minute

3) Any Stable AF with heart rate > 120 beats per minute would require intervention

4) Stable Paroxysmal AF (> 3 episodes within 24 hours, each with duration > 1 minute)

5) Stable AF > 2days (continuous or paroxysmal) would require anti-coagulation with oral coumadin as per our institution's pre-existing coumadin protocol unless there is contraindication for anticoagulation such as current or recent bleeding as determined by the patient's treating physician(s).

- Actual treatment received would be determined by the treating on-call team. Actual treatment used is not important to the primary end point of the study.

Appendix F: Sample size calculation.

The primary outcome is measured as the incidence of clinically important post-operative AF episodes in both the Amiodarone and placebo groups (proportions). Using Epi-Calc 2000 Software, version 1.02 (Brixton Health, UK), and assuming a drop in AF from 40% (control) to 20% (Amiodarone) with a beta error or 20% (power 80%) and Type I error (alpha) of 5% (2-sided), a total sample size of 162 was obtained (81 control and 81 experimental).

- To account for potential patient withdrawals due to drug side effects (maximum 18% in previous reports), 15 extra patients (18%) will be added to each arm of the trial leading to a total number of patients of 96 in each group.

Appendix G: Data Collection Forms

See attached samples

Appendix - G

Screening Case Report Form

Screening No: ____

Peri-operative Amiodarone in Cardiac Surgery Patients at High Risk for Atrial Fibrillation

Date Screened: ____/____/_____ (dd mm yyyy)

Patient Initials: ☐☐☐

UID: _____

Demographic Data	
Gender: 0☐ Male 1☐ Female	Date of Surgery ☐☐/☐☐/☐☐☐☐
D.O.B: ☐☐/☐☐/☐☐☐☐	Surgeon:
Referral Source: 0☑ Rounds 1☐ Triage Patient Location: 1☑ Home 2☐ Heart Institute 3☐ Other Institution	

Inclusion Criteria		
Elective Valve *or* Valve + Combined procedure *OR* LVEF ≤ 40%	0☐No	1☑Yes
Normal Sinus rhythm	0☐No	1☑Yes
≥ 18 years of age	0☐No	1☑Yes
Able to provide consent	0☐No	1☑Yes

Exclusion Criteria		
Resting HR < 60	0☑No	1☐Yes
SBP < 100	0☑No	1☐Yes
QTc > 450ms on baseline ECG	0☑No	1☐Yes
Hx Interstitial Lung Disease	0☑No	1☐Yes
Known sensitivity to Amiodarone	0☑No	1☐Yes
Hx Hypo/Hyperthyroidism	0☑No	1☐Yes
Unstable Angina *(emergent case)*	0☑No	1☐Yes
MI within 4 weeks of surgery	0☑No	1☐Yes
Heart Blocks *(1°, 2°, 3°)*	0☑No	1☐Yes
Current use of Class I/III antiarrythmics	0☑No	1☐Yes
Current use of Digoxin OR 2+ chronotropic agents	0☑No	1☐Yes
Chronic continuous atrial fibrillation	0☑No	1☐Yes
Planned AF Ablation	0☑No	1☐Yes

Late Exclusion: *For patients who were eligible but excluded pre-operatively, please indicate reason(s):*	
1☐	Patient Refused Participation
2☐	~~Surgeon Refused Patient Participation~~
3☐	Surgery Performed on the Weekend
4☐	Surgery Performed on an Emergent Basis
5☐	Pharmacy Unable to Dispense Study Drug
6☐	Enrolled in another perioperative trial Name of Trial:
7☐	Other:

Informed Consent	**Date**
Date of Informed Consent	11/12/2005

Randomization:		
0☐No	1☐Yes	After signing the informed consent, was the patient randomized?
If the patient was not successfully randomized, indicate reason:		
1☐		Patient Refused Participation
2☐		Surgeon Refused Patient Participation
3☐		Surgery Performed on the Weekend
4☐		Surgery Performed on an Emergent Basis
5☐		Pharmacy Unable to Dispense Study Drug
6☐		Patient Died Pre-operatively
7☐		Other:

Screening No: ____

Pre-op Case Report Form

Peri-operative Amiodarone in Cardiac Surgery Patients at High Risk for Atrial Fibrillation

Date of Form: ___/___/____ (dd mm yyyy)

Demographic Data

Patient Initials: ☐☐☐	Randomization #: ☐☐☐
UID: _____	Date of Surgery: ___/___/____ (dd mm yyyy)
Height: ☐☐☐.☐ cm	BMI: ☐☐
Weight: ☐☐☐.☐ Kg	BSA: ☐.☐☐ m^2

Medical History

Hypertension?	₀☐No	₁☐Yes
Hypercholestremia? *If Yes,*	₀☐No	₁☐Yes
Treated	₀☐No	₁☐Yes
Untreated	₀☐No	₁☐Yes
Obesity (BMI >30)?	₀☐No	₁☐Yes
History of smoking?	₀☐No	₁☐Yes
If yes, # Pack Years ☐☐☐.☐		
Is the patient a current smoker?	₀☐No	₁☐Yes
Angina?	₀☐No	₁☐Yes
If yes, CCS Class: ₁OI ₂OII ₃OIII ₄OIV		
Congestive Heart Failure?	₀☐No	₁☐Yes
If yes, NYHA Class: ₁OI ₂OII ₃OIII ₄OIV		
Previous MI?	₀☐No	₁☐Yes
If yes, dates of 3 most recent events: 1) ___/___/____ (dd mm yyyy)		
2) ___/___/____ (dd mm yyyy)		
3) ___/___/____ (dd mm yyyy)		
Valvular Heart Disease?	₀☐No	₁☐Yes
If yes,		
Mitral Regurgitation	₀☐No	₁☐Yes
Aortic Regurgitation	₀☐No	₁☐Yes
Mitral Stenosis	₀☐No	₁☐Yes
Aortic Stenosis	₀☐No	₁☐Yes
Cardiac Arrythmias < 6 months?	₀☐No	₁☐Yes
If yes,		
Atrial Fibrillation	₀☐No	₁☐Yes
Treatment: ₁OMeds ₂OCardioversion ₃OAblation ₄OOther		
VT/VF	₀☐No	₁☐Yes
Treatment: ₁OMeds ₂ODefibrillation ₃OPacing ₄OOther		

Intra-operative Procedure	
O	Isolated Mitral Valve: 1O Repair 2O Replacement
✓	Isolated Aortic Valve: 3O Repair 4✓ Replacement
O	Isolated Pulmonary/Tricuspid Valve: 5O Repair 6O Replacement
O	Combined Procedures: Valve Surgery *plus:* 7O CABG 8O Other Valve(s) 9O Ventricular Remodelling 10O VSD Repair 11O Aortic Root Procedure O Other:
12O	Ross Procedure
13O	Isolated Stentless Valve

Post-op Case Report Form

Peri-operative Amiodarone in Cardiac Surgery Patients at High Risk for Atrial Fibrillation

Date of Form: 24 / 05 / 2005
dd mm yyyy

Demographic Data

Patient Initials:	Randomization #:
UID:	Time of ICU Admission:

ICU Admission Bloodwork:

Hemoglobin *(g/L)*	132	☐ Not Done	Troponin T *(µg/L)*		☐ Not Done
Hematocrit *(%)*	38.9	☐ Not Done	CK *(U/L)*	418	☐ Not Done
Platelets *(x10⁹/L)*	136	☐ Not Done	INR	1.3	☐ Not Done
WBC's *(x10⁹/L)*	15.3	☐ Not Done	PTT	33	☐ Not Done
Na+ *(mmol/L)*	138	☐ Not Done	Fibrinogen *(U/L)*	2.3	☐ Not Done
K+ *(mmol/L)*	4.5	☐ Not Done	ALT *(U/L)*		☐ Not Done
Mg+ *(mmol/L)*	1.40	☐ Not Done	AST *(U/L)*		☐ Not Done
Cr *(mmol/L)*	91	☐ Not Done	HA1C		☐ Not Done
BUN *(mmol/L)*	3.5	☐ Not Done	Glucose *(mmol/L)*	6.6	☐ Not Done

Post-Operative Data *(mls)*

CT Drainage ~Admission~	1600	☐ Not Done	Colloid *(24hrs)*	0☐No 1☐Yes	
CT Drainage ~12-Hours~	910	☐ N/A	Crystalloid *(24hr)*	0☐No 1☐Yes	
CT Drainage ~24-Hours~	530	☐ N/A	D5W *(24hr)*	0☐No 1☐Yes	
Packed Cells *(# units)*	0☐No 1☐Yes		Pump Blood	0☐No 1☐Yes	
FFP *(# units)*	0☐No 1☐Yes		ACT	112	☐ Not Done
Platelets *(cc's)*	0☐No 1☐Yes		Protamine	0☐No 1☐Yes	50 mg
Cryo *(cc's)*	0☐No 1☐Yes		Cell Salvage	0☐No 1☐Yes	

Reoperation

Did the patient return to the OR?	0☐No 1☐Yes	Re-opening for:	1☐ Surgical Bleeding 2☐ Microvasc Bleeding 3☐ Graft Revision 4☐ Other:
Date of reoperation?	dd mm yyyy		

POD1 Bloodwork:

Hemoglobin *(g/L)*	116	☐ Not Done	Troponin T *(µg/L)*	☐☐☐.☐☐	☐ Not Done
Hematocrit *(%)*	34.2	☐ Not Done	CK *(U/L)*	419	☐ Not Done
Platelets *(x10⁹/L)*	142	☐ Not Done	INR	1.2	☐ Not Done
WBC's *(x10⁹/L)*	13.5	☐ Not Done	PTT	28	☐ Not Done
Na+ *(mmol/L)*	133	☐ Not Done	Fibrinogen *(U/L)*	☐☐.☐	☐ Not Done
K+ *(mmol/L)*	4.3	☐ Not Done	ALT *(U/L)*	☐☐.☐	☐ Not Done
Mg+ *(mmol/L)*	.94	☐ Not Done	AST *(U/L)*	☐☐.☐	☐ Not Done
Cr *(mmol/L)*	86	☐ Not Done	HA1C	☐☐.☐	☐ Not Done
BUN *(mmol/L)*	13.1	☐ Not Done	Glucose *(mmol/L)*	☐☐.☐	☐ Not Done

POD 2 Bloodwork:

Hemoglobin *(g/L)*	136	☐ Not Done	Troponin T *(µg/L)*	☐☐☐.☐☐	☐ Not Done
Hematocrit *(%)*	☐☐.☐	☐ Not Done	CK *(U/L)*	160	☐ Not Done
Platelets *(x10⁹/L)*	☐☐☐	☐ Not Done	INR	☐.☐	☐ Not Done
WBC's *(x10⁹/L)*	☐☐.☐	☐ Not Done	PTT	☐☐	☐ Not Done
Na+ *(mmol/L)*	☐☐☐	☐ Not Done	Fibrinogen *(U/L)*	☐☐.☐	☐ Not Done
K+ *(mmol/L)*	4.5	☐ Not Done	ALT *(U/L)*	☐☐.☐	☐ Not Done
Mg+ *(mmol/L)*	0.91	☐ Not Done	AST *(U/L)*	☐☐.☐	☐ Not Done
Cr *(mmol/L)*	96	☐ Not Done	HA1C	☐☐.☐	☐ Not Done
BUN *(mmol/L)*	3.5	☐ Not Done	Glucose *(mmol/L)*	6.1	☐ Not Done

POD 4 Bloodwork:

Hemoglobin *(g/L)*	☐☐☐	☐ Not Done	Troponin T *(µg/L)*	☐☐☐.☐☐	☐ Not Done
Hematocrit *(%)*	☐☐.☐	☐ Not Done	CK *(U/L)*	☐☐☐	☐ Not Done
Platelets *(x10⁹/L)*	☐☐☐	☐ Not Done	INR	☐.☐	☐ Not Done
WBC's *(x10⁹/L)*	☐☐.☐	☐ Not Done	PTT	☐☐	☐ Not Done
Na+ *(mmol/L)*	☐☐☐	☐ Not Done	Fibrinogen *(U/L)*	☐☐.☐	☐ Not Done
K+ *(mmol/L)*	☐☐☐	☐ Not Done	ALT *(U/L)*	☐☐.☐	☐ Not Done
Mg+ *(mmol/L)*	☐☐☐	☐ Not Done	AST *(U/L)*	☐☐.☐	☐ Not Done
Cr *(mmol/L)*	☐☐☐	☐ Not Done	HA1C	☐☐.☐	☐ Not Done
BUN *(mmol/L)*	☐☐☐	☐ Not Done	Glucose *(mmol/L)*	☐☐.☐	☐ Not Done

Operative Interventions:

ervention	Yes/No	Duration			
IAPB	0☐No 1☐Yes	☐☐☐ hrs	Inotropes	0☐No 1☐Yes	☐☐☐ hrs
Intubation	0☐No 1☐Yes	☐☐☐ hrs	Vasopressors	0☐No 1☐Yes	☐☐☐ hrs
BiPAP	0☐No 1☐Yes	☐☐☐ hrs	Peritoneal Dialysis	0☐No 1☐Yes	☐☐☐ days
LVAD	0☐No 1☐Yes	☐☐☐ hrs	Hemodialysis	0☐No 1☐Yes	☐☐☐ days
Swan Ganz	0☐No 1☐Yes	☐☐☐ hrs	TPN	0☐No 1☐Yes	☐☐☐ hrs

Post-Operative Complications			POD
Angina? *If yes,* CCS Class: 1○I 2○II 3○III 4○IV	0☐No	1☐Yes	
Myocardial Infarction?	0☐No	1☐Yes	
Death? *If yes, cause:*	0☐No	1☐Yes	
Cardiac Arrest? *If yes, cause:*	0☐No	1☐Yes	
Cardiac Arrythmias? *If yes,*	0☐No	1☐Yes	
Atrial Fibrillation Treatment: 1○Meds 2○Cardioversion 3○Ablation 4○Other	0☐No	1☐Yes	
VT/VF Treatment: : 1○Meds 2○Defibrillation 3○Pacing 4○Other	0☐No	1☐Yes	
Ischemic Stroke	0☐No	1☐Yes	
Hemorrhagic Stroke	0☐No	1☐Yes	
Respiratory Failure *(pO2/Fio2 Ration <150 or Re-intubation >24hrs)*	0☐No	1☐Yes	
Renal Failure *(dialysis dependant or Cr 2x baseline)*	0☐No	1☐Yes	
Hepatic Failure *(bilirubin >240)*	0☐No	1☐Yes	
Platelets < 20 x10^9	0☐No	1☐Yes	
Infection Requiring Treatment *If yes,* **Site:** 1○Mediastinitis 2○Pneumonia 3○Endocarditis 4○Leg Incision 5○Line Infection 6○Other	0☐No	1☐Yes	
Shock? *If yes,* **Type:** 1○Cardiogenic 2○Septic 3○Hypovolemic	0☐No	1☐Yes	

Comments:

Post-Operative Medications:

Calcium Channel Blockers			
Current Use	Drug	Daily Dose *(mg)*	Date Started
0 ○	None		dd/mm/yyyy
1 ○	Amlodipine	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
2 ○	Nifedipine	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
3 ○	Diltiazem	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
4 ○	Verapamil	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
5 ○	Other	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐

Ace Inhibitors			
Current Use	Drug	Daily Dose *(mg)*	Date Started
0 ○	None		dd/mm/yyyy
1 ○	Captopril	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
2 ✓	Enalapril	☐☐☐5 mg	☐☐/☐☐/☐☐☐☐
3 ○	Lisinopril	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
4 ○	Ramipril	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
5 ○	Other	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐

Anti-arrythmics			
Current Use	Drug	Daily Dose *(mg)*	Date Started
0 ✓	None		dd/mm/yyyy
1 ○	Digoxin	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
2 ○	Lidocaine	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
3 ○	Propafenone	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
5 ○	Other	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐

Beta-Blockers			
Current Use	Drug	Daily Dose *(mg)*	Date Started
0 ○	None		dd/mm/yyyy
1 ✓	Atenolol	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
2 ○	Metoprolol	☐☐50 mg	☐☐/☐☐/☐☐☐☐
3 ○	Acebutolol	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
4 ○	Carvedilol	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
5 ○	Other	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐

Anti-platelet Medications			
Current Use	Drug	Daily Dose *(mg)*	Date Started
0 ○	None		dd/mm/yyyy
1 ✓	ASA	☐☐81 mg	☐☐/☐☐/☐☐☐☐
2 ○	IIA/IIIB	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
3 ○	Plavix	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
4 ○	Other	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐

Anticoagulation Medications

Current Use	Drug	Daily Dose *(mg/units)*	Date Started
0 ○	None		dd/mm/yyyy
1 ○	Heparin	☐☐☐☐ units	☐☐/☐☐/☐☐☐☐
2 ○	Enoxaparin	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
3 ○	Fragmin	☐☐☐☐ iu	☐☐/☐☐/☐☐☐☐
4 ✓	Coumadin	☐ 7.5 mg	☐☐/☐☐/☐☐☐☐
5 ○	Other	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐

Diuretics

Current Use	Drug	Daily Dose *(mg)*	Date Started
0 ○	None		dd/mm/yyyy
1 ○	Furosemide	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
2 ○	Hydrochlorothiazide	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
3 ○	Spirolactone	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
4 ○	Other	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐

Inotropes / Vasopressors

Intra-op Use	Drug	Total Dose *(mg)*
0 ○	None	
1 ○	Dopamine	☐☐☐☐ mg
2 ○	Dobutamine	☐☐☐☐ mg
3 ○	Neosynephrine	☐☐☐☐ mg
4 ○	Levophed	☐☐☐☐ mg
5 ○	Epinephrine	☐☐☐☐ mg
6 ○	Other	☐☐☐☐ mg
7 ○	Other	☐☐☐☐ mg

Other Medications

Current Use	Drug	Daily Dose *(mg)*	Date Started
0 ○	None		dd/mm/yyyy
1 ○	Nitroglycerine	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
2 ○	Isordil	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
3 ○	Clonidine	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
4 ○	Insulin	☐☐☐ units	☐☐/☐☐/☐☐☐☐
5 ○	Glyburide	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
6 ○	Avandia	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
7 ○	Diamicron	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
8 ○	Metformin	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
9 ○	MgSO4	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
10 ○		☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
11 ○		☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
12 ○	Other	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
13 ○	Other	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐
14 ○	Other	☐☐☐☐ mg	☐☐/☐☐/☐☐☐☐

ECG (>24 hours post-op)	
Date of Post-Operative ECG	dd mm yyyy
Cardiac Rhythm Heart Rate: ☐☐☐ bpm	1☐ NSR 2☐ A-Fib 3☐ A-Flutter 4☐ SVT 5☐ 1° Heart Block 6☐ Mobitz I 7☐ Mobitz II 8☐ Paced
New q-waves?	0☐No 1☐Yes
If Yes,	
Anterior	0☐No 1☐Yes
Posterior	0☐No 1☐Yes
Inferior	0☐No 1☐Yes
Lateral	0☐No 1☐Yes

Amiodarone Administration				
POD	Date	Taken	Initials	Comments
1	08/03/2005	0☐No 1☐Yes	CW	
2	09/03/2005	0☐No 1☐Yes	CW	
3	10/03/2005	0☐No 1☐Yes	CW	
4	11/03/2005	0☐No 1☐Yes	CW	
5	12/03/2005	0☐No 1☐Yes	CW	

Discharge Information Data	
Date of ICU Discharge: ☐☐/☐☐/☐☐☐☐ 0☐N/A	Date of Hospital Discharge: ☐☐/☐☐/☐☐☐☐ 0☐N/A
Date of Transfer to Other Hospital: ☐☐/☐☐/☐☐☐☐ 0☐N/A	Date of Death: ☐☐/☐☐/☐☐☐☐ 0☐N/A

Primary Outcome

Atrial Fibrillation

Timeline	# Episodes	Duration	Treatment	Rx Type
1☐ OR Day			0☐No 1☐Yes ☐ NA	1☐ β Blockers 2☐Amiodarone 3☐ Digoxin 4☐ Ca+ Blocker 5☐ Pacing 6☐ Cardioversion 7☐ Other
2☐ POD 1			0☐No 1☐Yes ☐ NA	1☐ β Blockers 2☐Amiodarone 3☐ Digoxin 4☐ Ca+ Blocker 5☐ Pacing 6☐ Cardioversion 7☐ Other
3☐ POD 2			0☐No 1☐Yes ☐ NA	1☐ β Blockers 2☐Amiodarone 3☐ Digoxin 4☐ Ca+ Blocker 5☐ Pacing 6☐ Cardioversion 7☐ Other
3☐ POD 3			0☐No 1☐Yes ☐ NA	1☐ β Blockers 2☐Amiodarone 3☐ Digoxin 4☐ Ca+ Blocker 5☐ Pacing 6☐ Cardioversion 7☐ Other
4☐ POD 4			0☐No 1☐Yes ☐ NA	1☐ β Blockers 2☐Amiodarone 3☐ Digoxin 4☐ Ca+ Blocker 5☐ Pacing 6☐ Cardioversion 7☐ Other
5☐ POD 5			0☐No 1☐Yes ☐ NA	1☐ β Blockers 2☐Amiodarone 3☐ Digoxin 4☐ Ca+ Blocker 5☐ Pacing 6☐ Cardioversion 7☐ Other
6☐ POD 6			0☐No 1☐Yes ☐ NA	1☐ β Blockers 2☐Amiodarone 3☐ Digoxin 4☐ Ca+ Blocker 5☐ Pacing 6☐ Cardioversion 7☐ Other
7☐ POD 7			0☐No 1☐Yes ☐ NA	1☐ β Blockers 2☐Amiodarone 3☐ Digoxin 4☐ Ca+ Blocker 5☐ Pacing 6☐ Cardioversion 7☐ Other

2-3 Week Follow-up Case Report Form

Peri-operative Amiodarone in Cardiac Surgery Patients at High Risk for Atrial Fibrillation

Demographic Data	
Patient Initials: ☐☐☐	Randomization #: ☐☐☐
UID: _____	Date of F/U: ☐☐/☐☐/☐☐☐☐
Patient Location at 6 week F/U: 1☑UOHI 2○Home 3○ Other Hospital 4○ Convalescent Home 5○ GAU 6○ Deceased 7○ Lost to Follow-up 8○ Other	

Atrial Fibrillation @ 2-3-weeks	☐ Data Not Avail		Date
Did the patient experience A-Fib POD 7-21?	0☑No	1☐Yes	☐☐/☐☐/☐☐☐☐ *(1st Episode)*
If yes, was the patients re-admitted to Hospital for A-Fib POD 7-21?	0☑No	1☐Yes	☐☐/☐☐/☐☐☐☐ *(1st Readmission)*
If yes,: ☐Not Applicable **Total # Days in Hospital:** ☐☐			
Did the patient access a physician POD 7-21 for A-Fib?	0☑No	1☐Yes	☐☐/☐☐/☐☐☐☐ *(1st MD Visit)*
If yes,: **Emergency Department:**	☐No	1☐Yes	
# Visits: ☐☐			
Family Physician:	0☐No	2☐Yes	
☐Not Applicable **# Visits:** ☐☐			
Did the patient receive Rx for A-Fib POD 7-21? *If yes,* ☐Not Applicable	0☑None 1☐ β Blockers 2☐Amiodarone 3☐ Digoxin 4☐ Ca+Blocker 5☐ Pacing 6☐ Cardioversion 7☐ Other		☐☐/☐☐/☐☐☐☐ *(Treatment Started)*

[redacted] @ 2-3-weeks

	☐ Data Not Avail		Date
patient experience bleeding POD 7-21?	0☐No	1☐Yes	☐☐/☐☐/☐☐☐☐ (1st Episode)
If yes, was the patients re-admitted to Hospital for bleeding	0☐No	1☐Yes	☐☐/☐☐/☐☐☐☐ (1st Readmission)
If yes,:			
☐Not Applicable Total # Days in Hospital: ☐☐			
Did the patient access a physician POD 7-21 for bleeding?	0☐No	1☐Yes	☐☐/☐☐/☐☐☐☐ (1st MD Visit)
If yes,:			
Emergency Department:	☐No	1☐Yes	
# Visits: ☐☐			
Family Physician:	0☐No	2☐Yes	
☐Not Applicable # Visits: ☐☐			
Describe the patient's bleeding?	0☐No	☐Yes	☐☐/☐☐/☐☐☐☐ (Date of 1st Incident)
If yes,			
Late Tamponade	0☐No	1☐Yes	
Hemorrhagic Stroke	0☐No	2☐Yes	
Retroperitoneal Bleeding	0☐No	3☐Yes	
☐Not Applicable Other	0☐No	4☐Yes	

ECG	
Date of ECG	__/__/__ dd mm yyyy
Cardiac Rhythm	1O NSR 2O A-Fib 3O A-Flutter 4O SVT 5O 1° Heart Block 6O Mobitz I 7O Mobitz II 8O Paced
Heart Rate: ☐☐☐ bpm	
New q-waves?	0☐No 1☐Yes
If Yes,	
Anterior	0☐No 1☐Yes
Posterior	0☐No 1☐Yes
Inferior	0☐No 1☐Yes
Lateral	0☐No 1☐Yes

[redacted] Cardiovascular Society Functional Classification of Angina Pectoris

In order to assess another aspect of your quality of life, it is not only important to determine if you are having angina, but also to determine to what extent your angina affects your physical activities. In order to assess to what extent, if any, angina affects your physical activities, please help me the description that best fits you:

1☑ Class 1	**Ordinary physical activity are not limited by angina** • Angina may occur, but only if I am extremely active or if I am active for a very long period of time.
2☐ Class 2	**My physical activities are slightly limited by angina.** • I have angina if I walk uphill, climb two or more flights of stairs, walk outside in the cold or if I am upset or feel very stressed. • I would able to do my gardening or raking and walk at a brisk pace for at least 2 blocks on level ground without angina.
3☐ Class 3	**My physical activities are significantly limited by angina** • I have angina if I walk up one flight of stairs, or walk one block on level ground. • I would able to shower or dress myself without stopping, make a bed and play a game of bowling without angina.
4☐ Class 4	**I cannot perform any physical activities without having angina** • I may have may have angina at rest

New York Heart Association Functional Classification

SAY: In order to assess your quality of life, it is not only important to determine if you are having shortness of breath or if you are feeling tired (fatigued), but also to determine to what extent your shortness of breath and fatigue affect your physical activities. **Ordinary physical activities** are the routine activities in your day to day life (such as going up stairs, walking around the block) that you believe you should be able to do without any difficulty.

1☑ Class 1	**I have no limitation of my physical activity.** • Ordinary physical activity does not cause any unusual fatigue or shortness of breath.
2☐ Class 2	**My physical activities are slightly limited.** • I am comfortable at rest, but ordinary physical activities result in fatigue or shortness of breath.
3☐ Class 3	**My physical activities are significantly limited.** • I am comfortable only at rest, because small amounts of physical activity (less than ordinary activity) cause fatigue or shortness of breath.
4☐ Class 4	**I am unable to carry out physical activity without shortness of breath or fatigue.** • I have shortness of breath even at rest. • If I do any amount of activity, my symptoms get worse. • I am confined to a bed or chair

eding @ 6-weeks	☐ Data Not Avail		Date
d the patient experience bleeding after POD 21?	0☐No	1☐Yes	☐☐/☐☐/☐☐☐☐ (1st Episode)
If yes, was the patients re-admitted to Hospital for bleeding	0☐No	1☐Yes	☐☐/☐☐/☐☐☐☐ (1st Readmission)
If yes,:			
☐Not Applicable Total # Days in Hospital: ☐☐			
Did the patient access a physician after POD 21 for bleeding?	0☐No	1☐Yes	☐☐/☐☐/☐☐☐☐ (1st MD Visit)
If yes,:			
Emergency Department:	☐No	1☐Yes	
# Visits: ☐☐	0☐No	2☐Yes	
Family Physician:			
☐Not Applicable # Visits: ☐☐			
Describe the patient's bleeding?	0☐No	☐Yes	☐☐/☐☐/☐☐☐☐ (Date of 1st Incident)
If yes,			
Late Tamponade	0☐No	1☐Yes	
Hemorrhagic Stroke	0☐No	2☐Yes	
Retroperitoneal Bleeding	0☐No	3☐Yes	
☐Not Applicable Other	0☐No	4☐Yes	

ECG	
Date of ECG	dd / mm / yyyy
Cardiac Rhythm	1O NSR 2O A-Fib 3O A-Flutter 4O SVT 5O 1° Heart Block 6O Mobitz I 7O Mobitz II 8O Paced
Heart Rate: ☐☐☐ bpm	
New q-waves?	0☐No 1☐Yes
If Yes,	
Anterior	0☐No 1☐Yes
Posterior	0☐No 1☐Yes
Inferior	0☐No 1☐Yes
Lateral	0☐No 1☐Yes

anadian Cardiovascular Society Functional Classification of Angina Pectoris

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