University of Ottawa

Clinical Prediction Rule for the Development of New Onset Postoperative Atrial Fibrillation After Cardiac Surgery

by

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Abstract

This project set out to derive a prediction rule based on preoperative clinical variables to identify patients with high risk of developing atrial fibrillation following cardiac surgery. **Methods**: Prospectively collected data from a perioperative database was corroborated with chart review to identify eligible patients who had non-emergent surgery in 2010. Details on 28 preoperative variables were collected and significant predictors ($p<0.2$) were inserted into multivariable logistic regression and recursive partitioning. **Results:** 305 (30.5%) of 999 patients developed new onset postoperative atrial fibrillation. Eleven variables were significantly associated with atrial fibrillation, however, both final models included only three: left atrial dilatation, mitral valve disease and age. Bootstrapping with 5000 samples confirmed that both final models provide consistent predictions. Coefficients from the logistic regression model were converted into a simple seven point predictive score. **Conclusions:** This simple risk score can identify patients at higher risk of developing atrial fibrillation after cardiac surgery.

Executive Summary

Introduction: New onset postoperative atrial fibrillation (POAF) is common and associated with increased perioperative morbidity and long term mortality following cardiac surgery. This study describes POAF in a cardiac surgical center and derives a simple clinical prediction rule for identifying cardiac surgery patients at high risk for POAF based on two different statistical methods.

Methods: All patients without a history of atrial fibrillation (AF) who underwent non-emergent cardiac surgery in 2010 were included. Using prospectively collected data from a perioperative database, 28 preoperative variables were identified as potential predictors of POAF. The association between the predictors and POAF was determined by univariate analyses. Significant predictors ($p<0.2$) were used in two different methodologies; logistic regression and recursive partitioning to derive a clinical prediction rule with a threshold of 80% sensitivity. Internal validation was performed by bootstrapping. An atrial fibrillation risk score was devised from the final logistic regression model.

Results: Of the 999 patients included in the study, 305 (30.5%) developed POAF. Patients with POAF had a longer hospital stay (13.6 vs 8.1 days, $p<0.001$). They had more complications: pulmonary edema (OR 3.6, 95% CI 2.0-6.5), mesenteric ischemia (OR 5.7, 95%CI 1.1-29.9), acute renal failure (OR 1.9, 95% CI 1.3-2.9), gastrointestinal bleeds (upper GI tract: OR 4.6, 95% CI 1.4-5.5; lower GI tract: OR 11.6, 95%CI 1.3-99.2), readmission to ICU (OR 4.3, 95%CI 1.6-11.7) and in-hospital mortality (2.6% vs 0.1%, $p<0.0001$). Clinical predictors significantly associated with POAF were: age, renal failure, chronic obstructive pulmonary disease (COPD), hypothyroidism, New York Heart Association (NYHA) class heart failure, right ventricular dysfunction, left atrial dilatation,

valvular diseases, mitral valve disease, preoperative digoxin, surgery type, type of valve surgery and mitral valve surgery. The final logistic regression model included three variables: left atrial dilatation, mitral valve disease and age. The discrimination was fair with a c-statistic of 0.68 (95% CI 0.643-0.715). The model meeting the highest specificity and minimum sensitivity requirements using recursive partitioning included the same three predictors, providing a sensitivity of 84.6% (95%CI 79.9-88.4) and specificity of 39.5% (95% CI 35.8-43.2). The coefficients from the logistic regression model were converted into a simple point system for ease of use.

Conclusion: This simple risk score derived from two statistical methods can identify patients at higher risk of developing POAF. After prospective validation, it could be used to select patients in whom prophylactic treatment of atrial fibrillation has the greatest potential of benefit.

Table: Logistic Regression Model for Prediction of New Onset Postoperative Atrial Fibrillation

Variables	Beta-coefficient	Score
Intercept	-1.775	_
Age ≥ 65 years	0.945	3
Mitral valve disease		
Mild versus normal	0.494	1
Moderate-severe versus normal	0.970	3
Left atrial dilatation (> 41 mm)	0.352	1

Risk of POAF per score: 15.0% if 0, 19% if 1, 25% if 2; 32% if 3, 39% if 4, 48% if 5, 56% if 6 and 64% if 7

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Chapter 1: Introduction

1.1 Introduction to the Clinical Need for a Prediction Rule

After undergoing heart surgery, individuals often acquire an irregular heart rhythm that sometimes feels as a skipping of the heart. This irregularly irregular rhythm is called atrial fibrillation. Certain pre-existing conditions have been associated with an increased risk of developing atrial fibrillation after heart surgery, such as age, having had valve surgery and structural heart disease. This arrhythmia may not be permanent but having it at any time postoperatively, has been associated with increased hospital morbidity (more postoperative complications and longer hospital stay) and long term mortality, albeit the causal link is still unclear. The risk of developing this arrhythmia can be decreased by a variety of established methods, the easiest of which is to start prophylactic oral medications a few days before the surgery. However, this is not done routinely in many cardiac centers due to barriers in implementing such a broad program to all patients coming for surgery. It would be desirable to implement preventative measures in high risk patients and decrease the burden of atrial fibrillation postoperatively. Herein lays the need of developing a preoperative clinical prediction rule to identify this group of patients. The ideal prediction rule would be simple to use with only a few objective clinical variables and have a good sensitivity and the best possible specificity. Such a prediction rule could direct risk-adjusted treatment protocols to improve perioperative care of the cardiac surgery patient.

1.2 Goals and Objectives

- To describe the incidence and related perioperative course of new onset postoperative atrial fibrillation (POAF) after cardiac surgery at a single Canadian center.

- To determine the association between preoperative risk factors and the development of new onset atrial fibrillation requiring treatment in hospital after cardiac surgery.
- To use multivariable logistic regression and recursive partitioning to construct a sensitive and sufficiently specific preoperative clinical prediction rule to identify cardiac surgical patients at high risk for developing new onset postoperative atrial fibrillation.
- To perform internal validation of the prediction rule using bootstrapping techniques for both methods in the same cohort of patients.
- To calculate the sensitivity and specificity of the final prediction rule.
- To convert the logistic regression coefficients into a postoperative atrial fibrillation risk score to facilitate clinical implementation.

1.3 Description of Chapters of Thesis

The second chapter will review the current medical understanding of the pathophysiology of atrial fibrillation as well as the epidemiology of its presentation after cardiac surgery. The treatment for atrial fibrillation will be briefly outlined as well as some preventative measures that have been trialed. Finally a survey of recent literature will describe any existing risk indices or similar tools available to predict atrial fibrillation after heart surgery.

The third chapter will describe the methodological standards for derivation of the prediction rule. Subsequent to that, information about the institutional databases utilized for this study will be given. Details regarding choice of predictor variables, chart review and outcome assessment will be reported. Univariate analyses with the outcome of interest, new onset postoperative atrial fibrillation, and the procedures performed for both multivariable logistic regression and recursive partitioning will be detailed.

The results chapter will report the incidence of new onset postoperative atrial fibrillation in the study population as well as their course in hospital after heart surgery. Clinical outcomes after discharge from hospital for patients who developed postoperative atrial fibrillation will be reported. Univariate analyses results and the logistic regression model derivations will be discussed. The various models from recursive partitioning will be presented along with the final model. The outcomes from bootstrapping performed on both the logistic regression and recursive partitioning models will be described. The prediction score will be outlined with its predicted probabilities of developing postoperative atrial fibrillation.

The final chapter will close with a discussion about the analysis decisions, strengths and weaknesses of the study. Comparisons will be made with reported incidences, complications and risk indices and prediction rules. More importantly, the plans for the subsequent prospective validation with a new cohort of patients will be outlined.

Chapter 2: Background and Literature Review

2.1 Definition of Atrial Fibrillation

Atrial fibrillation is the most common irregular heart rhythm that starts in the atria and is described as being either controlled (heart rate <100 beats per minute) or uncontrolled (heart rate > 100 beats per minute) with varying effects on systemic blood pressure (Lip, Tse & Lane 2012). Patients have varied symptomatology related to their atrial fibrillation, some find it very debilitating while others do not notice its occurrence at all. The rhythm often starts off as an intermittent occurrence and may progress to persistent atrial fibrillation. The incidence of atrial fibrillation in the general population increases with age and is further increased by co-morbid diseases such as coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD) and renal failure (Skanes et al. 2012).

2.2 Pathophysiology of Atrial Fibrillation

As a result of improved surgical and perioperative care, patients undergoing cardiac surgery are older than a decade ago, with more co-morbidities contributing to their risk of developing postoperative atrial fibrillation (Jongnarangsin, Oral 2008). The causes of atrial fibrillation are not clearly elucidated (Maesen et al. 2012, Mathew, Patel & Joseph 2009). Suggested etiologies include chronic stress from diseases such as hypertension, diabetes mellitus, age related degeneration, fibrosis and conditions that cause atrial stretch (i.e. congestive heart failure, valvular disease or diastolic dysfunction) leading to abnormal remodeling of the heart. The etiology of postsurgical atrial fibrillation is probably multifactorial including factors that relate to: 1) the individual (genetic susceptibility, enhanced sympathetic

response, atrial remodeling and dilatation); 2) the surgery (incision of atria, manipulation, altered atrial electrophysiology, electrolyte disturbances, valve surgery); and 3) the postsurgical inflammatory process that is compounded in cardiac surgery patients who undergo cardiopulmonary bypass, a well-known trigger for release of inflammatory mediators (Levy, Tanaka 2003, Anselmi, Possati & Gaudino 2009, Banach et al. 2010).

Atrial electrophysiology can be altered secondary to ischemia, inflammation (Canbaz et al. 2008) and fibrosis which causes myocyte (heart muscle cell) breakdown and vacuole formation leading to areas of the atrium that are refractory to signal conduction. This insult causes patches of atria with varying refractory periods, a perfect set up for abnormal circulatory conduction pathways to develop and predispose a patient to arrhythmias (Hill, Kattapuram & Hogue 2002). Ak *et al* took right atrial biopsies from 100 patients undergoing coronary artery bypass grafting (CABG) and found that those who developed postoperative atrial fibrillation had a significantly higher percentage of apoptotic myocytes and large myolytic vacuoles (Ak et al. 2005). Even short periods of atrial fibrillation leads to remodeling of the myocardium (for as long as one week after conversion back to sinus rhythm), making each recurrence more difficult to convert back to a regular rhythm. This process leads to the natural progression of intermittent (or paroxysmal) to persistent atrial fibrillation.

In support of inflammation as a critical instigator of atrial electrophysiological remodeling, serum C-reactive protein levels (a marker of systemic inflammation) have been found to be higher in patients who develop atrial fibrillation compared to those with normal sinus rhythm (Anselmi, Possati & Gaudino 2009, Lahtinen et al. 2004). Various methods to modify the inflammatory response in cardiac surgery include performing off bypass surgery

(Abreu et al. 1999, Panesar et al. 2006), leukofiltration (filtering white blood cells) during bypass (Gunaydin et al. 2007), alternative strategies for delivery of cardioplegia (electrolyte solutions used to stop the heart on bypass), cardioplegia temperature (Adams et al. 2000) and cutting of the pericardium from behind to prevent pericardial effusions (Biancari, Mahar 2010). The fact that all these intraoperative measures have been associated with a reduced incidence of postoperative atrial fibrillation further supports the theory of inflammation as a significant contributor to its cause.

Atrial ischemia due to inadequate cardioplegia, surgical manipulation, dissection and atrial incisions also contribute to abnormal atrial substrate. Valve surgery involves cutting and placing sutures near and around the critical conduction pathways communicating between the atria to the ventricles (Sloan, Weitz 2001, Tselentakis et al. 2006). Perioperative swelling in the region of the atrioventricular node and along the valve annulus can cause temporary heart block requiring pacemaker insertion (Reade 2007a, Reade 2007b). Furthermore, placement of caval cannulae, pulmonary vein vents and transeptal approaches to valve surgery on the left side of the heart can all contribute to interruption of the blood supply or conduction system to the sinus node (Nair 2010).

Enhanced sympathetic response accompanied by withdrawal of modulators such as beta-blockers can lead to a heightened sympathetic response perioperatively. This hyper-adrenergic response has been identified as a contributor to the development of atrial fibrillation (Dimmer et al. 1998, de Leeuw et al. 1983). This is exemplified by the fact that chronic smokers appear to have a lower likelihood of developing atrial fibrillation (Mariscalco, Engstrom 2009). It is believed that due to chronic hyperadrenergic stimuli from the chemicals in tobacco smoke,

these patients are tolerant of the hypersympathetic state around the time of heart surgery (Kalman et al. 1995).

2.3 *Atrial Fibrillation after Cardiac Surgery*

Cardiac surgery exposes the patient to a very unique physiological state that further increases the risk of developing atrial fibrillation. Open heart surgery (procedures that involve cutting into the heart muscle) requires the use of cardiopulmonary bypass whereby the heart and lungs are arrested and the blood supply to the remainder of the body are supported by a roller pump. Coronary artery bypass grafting is performed on the epicardium (outside surface of the heart) and can be performed using the bypass machine or with the heart beating. The method depends on surgeon comfort, patient factors and the complexity of the surgery. In order to use the bypass machine, the patient must be given a potent anticoagulant, otherwise the blood would instantly clot on the oxygenating membrane. Passage of blood through this membrane causes gradual damage of clotting factors and also triggers an extensive inflammatory response. The longer the patient stays on cardiopulmonary bypass, the more significant the amount of bleeding and hypotension afterwards. Once heart lung bypass is established, the ventilator is turned off and the heart is arrested by means of administering a high potassium containing solution (cardioplegia) into the coronary arteries. After the surgical procedure is performed, weaning off the cardiopulmonary bypass circuit is performed by ventilating the lungs and reloading the heart. Once hemostasis is achieved, the sternum is closed and the patient is transferred to the intensive care unit. The two most common cardiac surgery procedures performed are coronary artery bypass grafting, valve replacement or a combination thereof.

The postoperative period after cardiac surgery has a high incidence of new onset atrial fibrillation, ranging from 23% in patients who have coronary artery bypass grafting to 45% in combination valve and bypass procedures (Mariscalco, Engstrom 2008). The peak incidence for the development of postoperative atrial fibrillation is between postoperative days two to four, and rarely occurring after a week (Shrivastava et al. 2009). The development of postoperative atrial fibrillation is associated with increased morbidity in the immediate postoperative period. An Italian study of 1832 patients found an increased incidence of stroke (3% vs 1%, p=0.0006), intra-aortic balloon pump use (5% vs 3%, p<0.005), infections (14% vs 10%, p=0.016) and respiratory failure (12% vs 5%, p<0.001) in patients with postoperative atrial fibrillation (Mariscalco et al. 2008). Similar findings were found in a Canadian center, with a significantly higher incidence of complications in patients who develop new onset postoperative atrial fibrillation (Kalavrouziotis, Buth & Ali 2007). After performing propensity matching, patients with new onset atrial fibrillation had a higher incidence of complications which included: stroke (2.8 vs 1.6%, p=0.006), gastrointestinal complications (4.2 vs 2.1%, p=0.002), deep sternal wound infections (1.3 vs 0.4%, p=0.012), sepsis (4.0 vs 1.1%, p<0.001), and renal failure (7.6vs 4.3% p<0.001); median hospital length of stay was prolonged (8 days vs 6 days, p=<0.001).

2.4 Long Term Implications

Treatment options after the development of atrial fibrillation include heart rate control and conversion back to regular sinus rhythm by means of medications or electrical cardioversion. Both intermittent and persistent atrial fibrillation are indications for systemic pharmacological anticoagulation to reduce the risk of a postoperative ischemic stroke (Rho 2009). The clinical prediction rule: CHADS2-VASc score is often utilized for patients with atrial

fibrillation to assess whether or not they should be started on oral anticoagulants, because atrial fibrillation is a major cause of ischemic strokes from blood clots that form inside the heart which embolize to the brain (Lip et al. 2010). Once the decision has been made to start anticoagulants, the management of this treatment is also fraught with challenges. Until recently, the most commonly used oral anticoagulant was coumadin, a drug that has varying effectiveness depending on diet, concomitant medications and patient compliance. The therapeutic window for coumadin is narrow and is monitored monthly using a blood test. Inadequate anticoagulation would not decrease the risk of embolic stroke and overdose of coumadin would lead to increased bleeding risks; the most significant of which are intracranial or large intra-cavitary hemorrhages. The emergence of newer agents in the recent years for the treatment of atrial fibrillation have boasted more stable therapeutic effects without the need for blood tests (Skanes 2012). This also implies that there is no means to test adherence in noncompliant patients. Another shortcoming of these new oral anticoagulants is the lack of an antidote (unlike coumadin), which would be needed in cases of overdose, bleeding or emergency surgery. Patients who develop complications from anticoagulation or failure of antiarrhythmic drugs may require another procedure involving radiofrequency or surgical ablation (Verma et al. 2011). The success rate of ablation is 75-90% after two procedures. Thus the management of atrial fibrillation has myriad of challenges that are balanced with the risk of common and sometimes life threatening complications.

Although the risk of short term morbidity is higher in patients with postoperative atrial fibrillation, no increase in the 30-day mortality was found in those patients after heart surgery (Bramer et al. 2010, Kalavrouziotis et al. 2009). However, studies looking at longer term outcomes have found an association with increased mortality. A long-term survival analysis

demonstrated an associated increase in mortality at four years from 13% to 26% in post-coronary artery bypass graft patients who developed atrial fibrillation compared to those who did not (Villareal et al. 2004). In another cohort of 1832 patients who underwent coronary artery bypass grafting, after a median follow-up of 51 months, the mortality rate of patients with new onset postoperative atrial fibrillation was significantly higher: 2.99 (95%CI: 2.33-3.84) per 100 person-years compared to 1.34 (95%CI: 1.05-1.71) per 100 person-years for those without atrial fibrillation (Mariscalco et al. 2008). Patients with atrial fibrillation were at higher risk of cardiac related death (54 embolic, 11 heart failure, 17 acute myocardial infarction). In a 10-year follow-up study of 6899 patients operated at the Baylor University Medical Center, patients with new onset postoperative atrial fibrillation (POAF) had an unadjusted survival of 52.3% (95%CI 48.4-56.0%) compared to 69.4% for those who did not have POAF (Filardo et al. 2009). Similarly, an analysis of data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database demonstrated a difference of 25% survival between coronary artery bypass grafting (CABG) patients with and without postoperative atrial fibrillation after a mean follow-up period of six years (El-Chami et al. 2010). The large size of that study (16169 patients) allowed the authors to demonstrate that the arrhythmia caused the survival curve to diverge even further with even higher mortality in certain patient subgroups, such as those prescribed warfarin (protective), women, Caucasians and those requiring surgery with cardiopulmonary bypass. This significant long-term mortality was associated with all patients who developed postoperative atrial fibrillation, not just those who left the hospital with the arrhythmia.

A similar trend was documented in 1039 patients undergoing aortic valve replacement with or without coronary bypass grafting; after ten years of follow-up, the adjusted hazard ratio for mortality was 1.48 (95% confidence interval: 1.12 to 1.96) for patients with new onset

postoperative atrial fibrillation in comparison to those without (Filardo, Adams 2010). However, Mahoney et al reported a hazard ratio of 1.19 (95% CI 1.09-1.3) in CABG patients and no difference for valve surgery patients (Mahoney et al. 2002).

The causes of death in the patients with postoperative atrial fibrillation (POAF) were more likely to be cardiac in origin. More studies are needed to determine if this association between atrial fibrillation and increased mortality is causal or if the development of POAF is a surrogate marker for patients with multiple comorbidities and risk factors making them at increased risk of dying postoperatively. Also, it is possible that the increased mortality is related to the treatment for chronic atrial fibrillation. Inadequate heart rate control or anticoagulation can lead to heart failure and embolic stroke. Conversely, over-anticoagulation can cause major bleeding into large compartments (thorax, abdomen, gastrointestinal) or into the head leading to hemorrhagic strokes. Regardless of the nature of the link between atrial fibrillation and increased mortality, decreasing the incidence of atrial fibrillation could shorten hospital length of stay and relieve some financial stresses on the current Canadian healthcare system. The next section will review some strategies to prevent postoperative atrial fibrillation.

2.5 *Current Interventions for the Prevention of Atrial Fibrillation*

Until the exact pathophysiology linking postoperative atrial fibrillation (POAF) with increased death rate is delineated, there is an onus on perioperative healthcare providers to minimize its occurrence. Studies have shown that prophylactic treatment can decrease not only the incidence of postoperative atrial fibrillation but also the length of stay in hospital (Gillespie et al. 2005). The prompt treatment of postoperative atrial fibrillation can decrease hospital stay and cost (average 1 day amounting to €1 800/patient), as demonstrated in a recent prospective

observational study from Italy where the incidence of atrial fibrillation was 30% (Rostagno et al. 2010).

Many interventions have been trialed to address prevention of postoperative atrial fibrillation (Bradley et al. 2005, Davis, Packard & Hilleman 2010, Crystal 2003). The majority of treatments involve medications to either control the heart rate or rhythm with varying success, using: beta-blockers (Celik et al. 2009, Iliuta et al. 2009, Merritt et al. 2003), amiodarone (Brantman, Howie 2006, Buckley et al. 2007, Daoud et al. 1997), diltiazem (Dobrilovic et al. 2005, Mikroulis et al. 2005), digoxin (Tokmakoglu et al. 2002), propafenone (Larbuisson, Venneman & Stiels 1996, Di Biasi et al. 1995) and verapamil (Auer et al. 2004). Other therapies target inflammatory mechanisms: HMG-CoA reductase inhibitors (also known as statins) (Kourliouros et al. 2008, Patel et al. 2007, Lertsburapa et al. 2008), corticosteroids (Baker et al. 2007), angiotensin-converting enzyme inhibitors (Healey et al. 2005), angiotensin receptor blockers (Ducharme et al. 2006, Healey et al. 2005), N-3 fatty acids (Calo et al. 2005, Heidarsdottir et al. 2010, Skuladottir et al. 2011) and naproxen (Cheruku et al. 2004). Performing coronary bypass grafting with beating heart surgery has also been compared to on-pump surgery. The odds ratio for developing postoperative atrial fibrillation on bypass was 7.4 (95% CI 3.4-17.9) compared to those who underwent surgery without cardiopulmonary bypass in a randomized control trial at the Bristol Heart Institute (Murphy et al. 2003). However, only select patients are able to have their heart surgery without the bypass machine.

With every therapy there needs to be a balance between efficacy and side effects. Intravenous magnesium sulfate has very few side effects and has been used to treat the dilutional hypomagnesemia that occurs after being connected to the bypass circuit (Aerra et al.

2006, Bert, Reinert & Singh 2001, Henyan et al. 2005, Miller et al. 2005) with varying results. Intravenous sodium nitroprusside infusions given over an hour after the cross clamp is removed during the bypass period has been shown to reduce the incidence of atrial fibrillation from 27% in placebo group to 12% (p=0.005) (Cavolli et al. 2008), but is balanced with the common risk of hypotension. Corticosteroids have a perceived borderline risk benefit ratio. A multi-center study of 241 coronary grafting patients in a randomized control trial administered intravenous hydrocortisone for three days starting the evening on the day of surgery demonstrated that the treatment lowered the incidence of postoperative atrial fibrillation by 18% (HR 0.54, 95%CI 0.36-0.82) (Halonen et al. 2007). The side effects of corticosteroid therapy include poor glucose control, increased immunosuppression leading to infections, gastrointestinal bleeding from peptic ulcers and acute psychosis. This study could not fully assess the safety of this drug because they excluded patients with diabetes, psychotic mental disorders, renal insufficiency, peptic ulcer disease, thrombophlebitis along with some other conditions. Although the absolute risk reduction of atrial fibrillation was 30% in a randomized control trial comparing treatment with one gram of methylpredinisolone with placebo, there was a higher incidence of major and minor complications in the treatment group (Prasongsukarn et al. 2005).

Having given a brief overview of the variety of interventions studied, we will limit our discussion below to the treatments that have a larger body of evidence and established efficacy. A systematic review of randomized control trials from the Cochrane database has concluded that beta-blockers, amiodarone, sotalol, and atrial pacing are all efficacious methods for the prevention of postoperative atrial fibrillation (Crystal et al. 2004a).

2.5.1 *Beta-blockers*

This aforementioned systematic review included 58 studies representing 8565 patients and showed that the most efficacious medical therapy studied were beta-blockers (administered at various times) with an odds ratio of 0.35 (95% CI> 0.26-0.49) (Crystal et al. 2004a). Comparisons within the class of beta-blockers, found carvedilol to be superior to metoprolol in decreasing the onset of atrial fibrillation (16% in carvediol vs 36% in metoprolol group) (Acikel et al. 2008). A multicenter open-label study comparing betaxolol and metoprolol in 1352 patients found that betaxalol significantly lowered the incidence of postoperative atrial fibrillation (12.0 vs 21.4%, p=0.0001) (Iliuta et al. 2009). The use of metoprolol for prophylaxis against atrial fibrillation as in the BLOS trial showed no decrease in hospital length of stay. In fact patients who were naïve to metoprolol had a longer hospital stay (183.4±171.2 hrs) compared to chronic users (148.0±59 hours, p=0.0002) (Connolly et al. 2003, Crystal et al. 2004b). That trial was also unique for showing a statistically significant increase in mechanical ventilation requirement for naïve beta-blocker users randomized to metoprolol (1.3% vs 0% in placebo, p=003). Despite those findings, the American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery state that there is a substantial body of evidence for the efficacy of prophylactic beta-blocker use (Bradley et al. 2005).

2.5.2 *Amiodarone*

Amiodarone is a Vaughan-Williams Class III antiarrhythmic drug in the category of potassium channel blockers. The prophylactic use of oral amiodarone, given preoperatively was shown not only to decrease the incidence of symptomatic atrial fibrillation (4.2 vs 18.0%,

p=0.001) but also ischemic strokes (1.7% vs 7.0%, p=0.04) and ventricular tachycardia (1.7% vs 7.0%, p=0.04) (Giri et al. 2001). Similar results were also found in a randomized control trial where oral amiodarone was added to beta-blockers in the elderly (mean age 72±6.7 years old) preoperatively (Kluger, White 2003). Guarnieri *et al* demonstrated a decrease in the incidence of atrial fibrillation from 67/142(47%) in the placebo group to 56/158(35%) after surgery by administering 1 gram per day of intravenous amiodarone for two days after heart surgery. However, such treatment did not decrease the length of hospital stay (Guarnieri et al. 1999). The PAPABEAR protocol involved administering oral amiodarone for 6 days before and after surgery. This randomized control trial that stratified 600 patients for age, surgical procedure and preoperative treatment with beta-blockers reported a hazard ratio of 0.52 (95%CI 0.34-0.69) in favor of amiodarone versus placebo. They had complete follow-up and were able to demonstrate that at one year there was no difference in either hospital readmission or mortality (Mitchell et al. 2005). The combination of 48 hours of intravenous amiodarone infusion started on call to the operating room and oral amiodarone during the following three days (Kerstein et al. 2004) was effective in a small study of 51 patients. This combination of intravenous amiodarone with oral conversion negates the six day loading that is required in the PAPABEAR protocol and allows for prophylaxis treatment in patients who have urgent or even emergent surgery. A meta-analysis has shown that amiodarone decreases the incidence of ventricular tachycardia, fibrillation and neurological events (Bagshaw et al. 2006). The body of evidence favoring the prophylactic use of amiodarone is such that some centers have developed protocols to prevent postoperative atrial fibrillation (POAF) using amiodarone, especially in hemodynamically unstable patients (Khanderia et al. 2008). Unfortunately, amiodarone is associated with multiple side effects and drug interactions (Rho 2009), the most serious being:

hypotension, bradycardia, lung toxicity, worsening arrhythmias, thyroid derangements, liver injury, photosensitization, skin and corneal deposits (Patel et al. 2006). The number of complications reported in clinical trials for prevention of POAF is insignificant. However, this might be explained by the small sample sizes of those studies, probably not powered to assess safety. Amiodarone is the only drug given for prophylaxis against atrial fibrillation that has been shown to decrease the length of hospital stay in some studies (Aasbo et al. 2005).

2.5.3 *Sotalol*

Sotalol is also a Vaughan-Williams Class III anti-arrhythmic with some enhanced Class II (beta-blockade) characteristics, and is primarily excreted by the kidneys. Clinically, it is now used as a racemic mixture because the enantiomer d-sotalol (pure potassium channel blocker with no beta-blocker activity) was found to have an associated increased in mortality secondary to arrhythmias in patients with ventricular dysfunction after myocardial infarctions (Waldo et al. 1996). A randomized control trial of 85 patients undergoing coronary artery bypass grafting demonstrated a lower incidence of atrial fibrillation in patients administered sotalol (12.5%) 24-48 hours before surgery versus placebo (38%, p=0.008) (Gomes et al. 1999). In a larger study of 255 patients, those randomized to receive sotalol two hours before heart surgery were found to have a decrease in supraventricular tachyarrhythmias (82% of which were atrial fibrillation) from 46% in placebo to 26% ($p<0.0001$) (Pfisterer et al. 1997). Although this study reports a shorter length of hospital stay, the study included individuals with a history of supraventricular tachyarrhythmias and the primary outcome was not exclusively atrial fibrillation. A meta-analysis comparing amiodarone to sotalol, concluded that there was no difference between the two drugs for efficacy in reducing the incidence of atrial fibrillation after heart surgery (Wurdeman et al. 2002). Similarly, a randomized control trial comparing sotalol to amiodarone

found no difference in the incidence of atrial fibrillation after coronary artery bypass grafting surgery. However, patients treated with sotalol required more inotropic and vasopressor support and had a greater need for pacing (Mooss et al. 2004). Despite its proven efficacy sotalol is not used because its administration is associated with a 2.4-6% incidence of torsade de pointes, a malignant arrhythmia, that may cause cardiac arrest, especially in women and patients with low ventricular function (Elming et al. 2004). General use of sotalol in cardiac surgery is also limited due to the high incidence of renal impairment after cardiopulmonary bypass (Garwood 2004) leading to higher serum levels of the drug.

2.5.4 *Atrial Pacing*

Alternatively, electrical stimulation of the atrial muscle via internally placed wires is the most common non-pharmacological method to prevent of atrial fibrillation. A technique termed "overdrive pacing" is used to set the heart rate higher than the native rhythm, which does not allow the atrial substrate any time to assume an irregular rhythm. Continuous dynamic overdrive pacing can reduce the incidence of atrial fibrillation from 27% to 10% (p=0.036) (Blommaert et al. 2000). Variations in pacing wire insertion routes or sites and algorithms for pacing have been the subject of many investigations (Archbold, Schilling 2004, Gillis, Kerr & Crystal 2005, Fan et al. 2000). Intrathoracic biatrial wires have been implanted for use in cardioverting patients who develop atrial fibrillation postoperatively (Dzemali et al. 2006). A randomized study comparing two right atrial pacing strategies versus placebo failed to show any decrease in postoperative atrial fibrillation (Hakala et al. 2005). Daoud *et al* performed a meta-analysis to conclude that biatrial overdrive pacing (OR 2.6; 95%CI 1.4-4.8), fixed high rate right atrial overdrive (OR 1.8; 95%CI 1.1-2.7) and fixed high rate biatrial pacing more than halved the risk of atrial fibrillation (Daoud et al. 2003). With regard to safety, the presence of the wires

directly on the heart can in themselves stimulate arrhythmias (Chung et al. 2000). The AFIST II trial compared amiodarone alone, atrial septal pacing alone or both for atrial fibrillation prophylaxis found that the combination of amiodarone and pacing was the best strategy for prevention (White et al. 2003). Based on currently available evidence, biatrial pacing is recommended for atrial fibrillation prophylaxis by the American College of Chest Physicians (Maisel, Epstein & American College of Chest 2005).

2.5.5 *Summary of the Interventions to Prevent Atrial Fibrillation*

The recommendations by the American College of Cardiology/American Heart Association/European Society of Cardiology suggest, in order of efficacy, amiodarone, sotalol and beta-blockers for atrial fibrillation prophylaxis (Shrivastava 2009). With regard to safety however, the order is changed to beta-blockers, amiodarone, sotalol. The guidelines indicate that the use of beta-blockers has a class 1A evidence level, amiodarone, has a class IIA level and sotalol has a class IIB (Fuster et al. 2011). The American College of Chest Physicians also added biatrial pacing as an effective therapy for prevention of postoperative atrial fibrillation, strength of recommendation, B with good grade of evidence and small amount of net benefit (Maisel et al. 2005). The Canadian Cardiovascular Society (CCS) Consensus recommends Class IIa for amiodarone prophylaxis for patients who are beta-blocker naïve (Mitchell et al. 2011). This would make amiodarone the agent of choice for prophylaxis in the case of urgent or emergent procedures.

2.6 *Need for Preoperative Clinical Prediction Rule*

Despite having evidence supporting the efficacy of prophylactic treatment for postoperative atrial fibrillation, initiation of medications before cardiac surgery is not a common

practice. This is exemplified by a recent survey of Canadian cardiac surgeons which revealed that only 58% of surgeons used beta-blockers and 19% used amiodarone for prophylaxis. The most common barrier to wide-spread prophylaxis was excessively complicated implementation of preoperative administration (Price et al. 2009). Prescription of oral medications would require that the patients be seen multiple times in clinic, well in advance of the surgical date, to allow for titration of new medications and monitoring for their side effects. This is further complicated by the fact that heart surgery is often not planned until the patient presents with symptoms and is discovered to have disease requiring urgent surgery. Obtaining therapeutic plasma levels of drugs can be quicker with intravenous administration, however this would require admission into hospital before surgery, occupying beds in already overly crowded hospitals. Assuming the true incidence of postoperative atrial fibrillation is approximately 25%, a blanket prevention scheme for all comers is not practical or cost-effective. In this situation, targeting high risk patients may maximize the limited health care resources available. Mahoney *et al* reported cost effectiveness of targeting prophylactic intravenous amiodarone in higher risk patients for the prevention of atrial fibrillation (Mahoney et al. 2002). Higher risk patients included those who were older (particularly with a history chronic obstructive pulmonary disease) undergoing valve or combination cardiac surgery. They estimated the cost of developing postoperative atrial fibrillation ranged from $2 857 (SD 932) to $4 536(SD 1441) in patients having combination (CABG and valve) procedures.

The recommended treatments to prevent perioperative atrial fibrillation are considered safe for short term use (Shrivastava et al. 2009). However, many complications and side effects associated with those treatments mandates the identification and targeting of patients at higher risk of developing postoperative atrial fibrillation (POAF) to achieve the best possible risk

benefit ratio of preventative therapy. Since most effective preventative therapies of POAF must be started before or during cardiac surgery, it is important to identify patients at moderate to high risk before surgery. A clinical prediction rule is the tool best suited to identify these high risk patients.

Clinical prediction rules are tools often used by emergency physicians in busy clinical settings as an aid to predict a diagnosis (a prediction rule) or direct management (a decision rule). The use of such rules can help improve efficiency without imparting harm on the patient (Perry et al 2006, Philips et al 2010). Clinical situations where rules have been developed include: when to image injured ankles (Stiell et al 1996), when to stop resuscitation efforts in hospital (van Walraven et al 1999), when to start blood thinners on patients with atrial fibrillation (Lip 2010), when early discharge is safe for patients who present with chest pain (Christensen et al 2006) or when to perform a chest x-ray (Hess et al 2010). Other rules have been designed to help predict the likelihood of certain diagnoses such as: severe community acquired pneumonia (Espana et al 2006), adverse outcomes after coronary artery bypass surgery (Fortescue et al 2001), and pulmonary embolism (Wells et al 2000). In place of anecdotal expert opinion, prediction rules are derived from the best available evidence with methodological guidelines for derivation and validation (Stiell, Wells 1999, Laupacis et al 1997, Wasson et al 1985).

Postoperative atrial fibrillation (POAF) is a common disease associated with significant morbidity and long term mortality; although preventative treatments are effective, they can cause a small degree of harm. This situation highlights the need for a predictive model for POAF in order to tailor patient care for those who would most benefit from treatment. The derivation of a model for postoperative atrial fibrillation has been the subject of interest for many

investigators. An ideal prediction rule should be simple with as few variables as possible and not involve any extra calculations or embedded scores. Preferably the rule should include variables that can be objectively and consistently evaluated, as well as be easily obtainable in many different clinical settings. Generalizability of the rule is desired, otherwise widespread implementation of the rule will be difficult.

2.7 *Predicting Postoperative Atrial Fibrillation*

2.7.1 *Risk Factors Associated with Postoperative Atrial Fibrillation*

Multiple centers have performed multivariable analyses to determine the risk factors associated with the development of postoperative atrial fibrillation (Table 1). Age is the most consistently confirmed risk factor for developing atrial fibrillation (Amar et al. 2002). Sex has mixed reports of either male (Mahoney et al 2002) or female (Rostagno et al 2010) being at higher risk. The analyses of race demonstrated that being African American is protective against acquiring the arrhythmia with an odds ratio of 0.539 (95% 0.374-0.77, p=0.001) (Lahiri et al. 2011). In fact, the Caucasian race has an odds of 1.74 (95%CI 1.7-1.78) of developing postoperative atrial fibrillation when compared to black citizens and other non-Caucasians in the United States (Rader et al. 2011). The list of preoperative predictors includes a large number of expected cardiovascular characteristics such as coronary artery disease (Echahidi et al 2007), reduced ejection fraction (El Chami et al 2010), congestive heart failure (Mathew et al 1996), mitral valve disease (Da Silva et al 2010) and history of atrial fibrillation (Rostagno et al 2010). Diseases of other major organ systems have also been associated with postoperative atrial fibrillation (POAF): chronic obstructive pulmonary disease (El-Chami et al 2010), obesity (Elchahidi eta l 2007), diabetes mellitus (El-Chami et al 2010) and renal insufficiency (Thoren et al 2012). Studies

have also implicated intraoperative factors that lead to an increased incidence of POAF: type of surgery (coronary versus valve) (Mariscalco et al 2008), repeat operations (Asher et al 1998), the urgency of surgery (El-Chami et al 2010), length of time spent on bypass (Scherr eta l 2006), complicated weaning off the heart lung machine (Mariscalco et al 2008) and even type of atrial cannulation (Mathew 1996). Postoperative variables also have been listed as predictors of postoperative atrial fibrillation, but these variables would not be available for consideration before the time surgery.

Table 1

Highlighted Reported Predictors of Increased Risk of Postoperative Atrial Fibrillation

	Number of Patients	Surgery Type	Timeline[§]	Author	Year
Age	8709	CABG	R	Mahoney	2002
	1217	Valve	R	Mahoney	2002
	624	Combo	R	Mahoney	2002
	253		P	Auer	2005
	16169	CABG	R	El-Chami	2010
	680		R	Kourliouros	2008
	4657		P	Mathew	2004
	18 517	CABG	R	El-Chami	2012
	2417		P	Mathew	1996
	358	CABG	P	Zaman	2000
	7115	CABG	R	Thoren	2012
Age > 50 years	5085	CABG, age >50	R	Echahidi	2007
Age ≥ 60 years	7347	Valve	R	Kalavrouziotis	2007
Age > 70 years	8434		R	Mariscalco	2008
	1078		R	Scherr	2006
Age>75 years	915		R	Asher	1998
	452		P	Da Silva	2010
Age >80 years	725		P	Rostagno	2010
Male	8709	CABG	R	Mahoney	2002
	5085	CABG, age >50	R	Echahidi	2007
	7347		R	Kalavrouziotis	2007
	2417	CABG	P	Mathew	1996
	168	CABG	P	Mendes	1995
	368	CABG	P	Zaman	2000
	7115		R	Thoren	2012
Female	725		P	Rostagno	2010
Caucasian	16169	CABG	R	El-Chami	2010

COPD	1217 5085 16169 7347 4657	Valve CABG CABG	R R R R P	Mahoney Echahidi El-Chami Kalavrouziotis Mathew	2002 2007 2010 2007 2004
Smoker	1217 16169 7115	Valve CABG CABG	R R R	Mahoney El-Chami Thoren	2002 2010 2012
Hypertension	5085 16169	CABG, age >50 CABG.	R R	Echahidi El-Chami	2007 2010
Any valve disease	16169	CABG	R	El-Chami	2010
Obesity (BMI>30kg/m^2)	5085	CABG, age >50	R	Echahidi	2007
Height (cm)	18 517	CABG	R	El-Chami	2012
Weight (kg)	18 517	CABG	R	El-Chami	2012
Metabolic syndrome	5085	CABG, age <50	R	Echahidi	2007
Diabetes	16169	CABG	R	El-Chami	2010
Left atrial size >40 mm	725 915		P R	Rostagno Asher	2010 1998
Myocardial infarction MI within 7 days	16169 7347	CABG	R R	El-Chami Kalavrouziotis	2010 2007
Triple vessel coronary artery disease	5085	CABG, age >50	R	Echahidi	2007
Previous MI	8709 7115	CABG CABG	R R	Mahoney Thoren	2002 2012
Left main CAD	16169	CABG	R	El-Chami	2010
Severe RCA occlusion	168	CABG	P	Mendes	1995
Ejection fraction	16169	CABG	R	El-Chami	2010
Congestive heart failure	16169 2417	CABG	R P	El-Chami Mathew	2010 1996
NYHA class	8434 7115	 CABG	R R	Mariscalco Thoren	2008 2012
Mitral valve disease	452		P	Da Silva	2010
Peripheral vascular disease	16169 18517	CABG CABG	R R	El-Chami El-Chami	2010 2012
History of atrial fibrillation	725 4657 1078 2417		P P R P	Rostagno Mathew Scherr Mathew	2010 2004 2006 1996
p-wave > 155 ms on electrocardiogram	358	CABG	P	Zaman	2000
No preop beta-blocker	253 452		P P	Auer Da Silva	2005 2010
Heart rate >100bpm	2417		P	Mathew	1996
Beta-blocker use	1078		R	Scherr	2006
Digoxin use	1078		R	Scherr	2006
No preop statin use	680		R	Kourliouros	2008
Previous stroke	16169 7347	CABG	R R	El-Chami Kalavrouziotis	2010 2007
Low HDL	5085	CABG, age >50	R	Echahidi	2007

Creatinine level	16169	CABG	R	El-Chami	2010
Renal insufficiency	624 16169 7115	Combo CABG CABG	R R R	Mahoney El-Chami Thoren	2002 2010 2012
Dialysis	16169	CABG	R	El-Chami	2010
Type of surgery	8434		R	Mariscalco	2008
Valve surgery	253 4657 1078		P P R	Auer Mathew Scherr	2005 2004 2006
Mitral stenosis	915	Valve	R	Asher	1998
Valve & CABG surgery	725 7347 1078		P R R	Rostagno Kalavrouziotis Scherr	2010 2007 2006
Non-elective surgery	16169	CABG	R	El-Chami	2010
On-bypass surgery	1078		R	Scherr	2006
Reoperation	915	Valve	R	Asher	1998
Bypass time	8709 5085 1078 2417	CABG CABG, age >50	R R R P	Mahoney Echahidi Scherr Mathew	2002 2007 2006 1996
Hypothermia	915	Valve	R	Asher	1998
Pulmonary vein venting	2417		P	Mathew	1996
Bicaval venous cannulation	2417		P	Mathew	1996
Complicated weaning off CPB	8434		R	Mariscalco	2008
Temporary pacing	8434		R	Mariscalco	2008
Inotropic support	8434		R	Mariscalco	2008
Milrinone*	232		P	Fleming	2008
Withdrawal of beta-blocker	4657		P	Mathew	2004
Withdrawal of ACEi	4657		P	Mathew	2004
Fluid balance >1.5L	452		P	Da Silva	2010
Atrial pacing	2417		P	Mathew	1996

§R=retrospective P=prospective study; CABG= coronary artery bypass grafting; BMI= body mass index; MI= myocardial infarction; CAD=coronary artery disease; RCA=right coronary artery; NYHA=New York Heart Association class heart failure; ECG=electrocardiogram; HDL=high density lipids; CPB=cardiopulmonary bypass; ACEi=angiotensin converting enzyme inhibitor; ms=milliseconds; *randomized trial, all other studies were observational in nature

The presence of preoperative atrial fibrillation is an established risk factor for the development of postoperative atrial fibrillation (Ngaage et al. 2007). The risk of having major cardiovascular complications increased from 52% to 70% ($p<0.0001$) in patients with preoperative atrial fibrillation. As in previous reports, there was no significant increase in operative mortality

(1.6% vs 1.9% in preoperative atrial fibrillation patients, p=0.79) but the median 6.7 years mortality from all causes was 40% higher, p=0.02. Pre-existing atrial fibrillation before cardiac surgery also increases the following complications postoperatively: low cardiac output, delirium and stroke, all leading to an increased mortality (Banach et al. 2008). A retrospective analysis of 46 984 patients who underwent coronary artery bypass grafting at the Cleveland Clinic Foundation from 1972 to 2000 found the same concerning trend (Quader et al 2004). That study used propensity score matching to compare the survival of patients with preoperative atrial fibrillation and those who did not in an average follow-up period of 12.6 years. The survival difference between those with and without preoperative atrial fibrillation was reported 17% at 5 years, 24% at 10 years and 23% at 15 years. This marked increase in mortality outweighs the small risk of complications associated with preventative therapy for postoperative atrial fibrillation. This risk is so high that a prediction rule is not needed to direct therapy for patients with preoperative atrial fibrillation. Therefore, the population that would most benefit from a prediction rule would be those who will have new onset postoperative atrial fibrillation after undergoing heart surgery.

2.7.2 *Prediction Models for New Onset Postoperative Atrial Fibrillation*

The purpose of this project was to derive a simple clinical rule consisting of only preoperative variables to predict new onset postoperative atrial fibrillation. Other researchers have approached this topic and have derived prediction rules or risk indices for postoperative atrial fibrillation. However, there are no reports that suitably fulfill our criteria for a clinical prediction rule. In this section a discussion of the current models predicting postoperative atrial fibrillation after heart surgery will be presented in terms of why they are inapplicable to the purposes of this study.

Most previous prediction models utilized variables obtained intraoperatively or postoperatively which are not foreseeable at the onset of surgery. Since most of the prophylaxis treatments for atrial fibrillation need to be given before surgery, the use of these variables would not allow for the opportunity to start prophylaxis in time to decrease the incidence of postoperative atrial fibrillation. For example, in a small study of 253 cardiac surgery patients with normal ventricular function, the model derivation included postoperative complications (stroke, infections, unstable hemodynamics) in their multivariable logistic regression analysis (Auer et al. 2005). Similarly, Matthew *et al* derived a risk index for atrial fibrillation from observational data of 4657 patients who underwent coronary artery bypass grafting in 70 international centers. Included in the list of predictors were postoperative withdrawal of beta-blockers (OR 191;95% CI 1.52-2.40) or angiotensin-converting enzyme inhibitors (OR 1.69;95% CI 1.38-2.08) (Mathew et al. 2004). Mariscalco *et al* reviewed 8434 procedures performed over a ten year period, looking at 35 variables to identify risk factors for developing atrial fibrillation for different types of surgeries (coronary artery bypass grafting, aortic valve replacement and combination). The models included postoperative variables such as: need for temporary pacing after surgery, need for inotropic support and difficulty weaning off the heart-lung machine (Mariscalco, Engstrom 2008).

Other studies exclude patients that constitute a large proportion of the population undergoing heart surgery, limiting the generalizability of the rule. Banach *et al* delineated separate risk factors for postoperative atrial fibrillation (POAF) in 300 patients undergoing aortic valve replacement for regurgitation and stenosis (Banach et al. 2007). For patients with aortic stenosis, predictors of POAF included age ≥ 70 years, extremes of body mass index, low ventricular function and specific echocardiographic measurements. The study excluded patients

with history of ischemic heart disease, stroke, minimally invasive heart or vascular surgery, infected valves, urgent or emergent surgery, patients on antiarrhythmics including beta-blockers and any important systemic illness. This long list of exclusion criteria would make this model inapplicable to more than half the population cared for by most cardiac surgical centers.

As mentioned in the previous section, the presence of preoperative atrial fibrillation is a significant risk factor for developing the arrhythmia after surgery and should be given prophylactic treatment without the use of a prediction rule. Any studies that include this variable are not focusing on the right patient group. For instance, Amar *et al* reported prediction rule derived from clinical and electrocardiogram (ECG) variables including age (OR 1.1 per year increase; 95%CI 1.0-1.1) and P-wave on ECG of >110ms (OR 1.3; 95%CI 1.1-1.7) but also a history of previous atrial fibrillation (OR 3.7; 95% CI 2.3-6.0), and low cardiac output postoperatively (OR 3.0; 95%CI 1.7 to 5.2) (Amar et al. 2004). Very recently a group in Sweden studied a cohort of 7115 coronary artery bypass patients and derived a rule using logistic regression composed of only preoperative variables: age, preoperative serum creatinine levels, sex, New York Heart Association heart failure class III or IV, smoking, previous myocardial infarction and normal lipid levels. That study also included patients with a history of atrial fibrillation who were in normal sinus rhythm at the time of surgery (Thoren et al. 2012). Although the model used only preoperative variables no validation study was carried out and should be performed as the next important step in prediction rule methodology.

Another atrial fibrillation risk index was published within the last year. It was derived using 18 517 CABG patients from the Society of Thoracic Surgeons' national database and validated with a subsequent sample of 1378 patients from the same database (El-Chami et al.

2012). Mulitivariable logistic regression was used to derive the model. Even though the univariate analysis revealed 25 significant predictors of atrial fibrillation ($p<0.05$), only four were included in the final logistic model. Univariate analysis revealed that age was the most predictive of atrial fibrillation with an odds ratio of 1.059 per year increase in age (95% CI, 1.055-1.063). Other interesting predictors in the final model were height (172.3 versus 171.2 cm in those without atrial fibrillation) and weight (86.8 vs 85.7 kg in those without atrial fibrillation) but not body mass index. Height and weight have never been reported to have an association with atrial fibrillation, although body mass index has (Elchahidi 2007). This raises the concern that the inclusion of height and weight might have been statistically driven as opposed to clinical plausibility. Such a small difference in height and weight does not have a clear pathophysiological link to postoperative atrial fibrillation. The fourth variable contributing to the model calibration was presence of peripheral vascular disease. The authors then converted the beta coefficients into a risk score with four components, naming it the AF risk index. The approach taken by this team of investigators was similar to the plan for this thesis project. Differences however are 1) we planned to include both coronary bypass and valve surgery patients in order to make the prediction rule more generalizable; 2) our prediction rule will be derived from multivariable logistic regression and recursive partitioning; 3) rule validation will be performed by bootstrapping with replacement when resampling from the derivation cohort. We shall compare our results with El-Chami's study in Chapter 5.

To summarize, postoperative atrial fibrillation has been shown to be associated with an increase in perioperative morbidity and long-term mortality. There are established treatments available for the prevention of atrial fibrillation, namely beta-blockers, amiodarone, sotalol and atrial pacing. In order to balance the risk benefit ratio of these treatments, it would be useful to

predict and provide prophylaxis to those at high risk of developing the arrhythmia after cardiac surgery. None of the previous tools are clinical useful. They either contain variables that cannot be collected preoperatively, target the wrong patient population or include variables which are not clinically significant. The aim of our study is to derive a simple clinical prediction rule to predict new onset postoperative atrial fibrillation after cardiac surgery using strictly preoperative variables. This rule would then allow for implementation of an atrial fibrillation prevention protocol to decrease the incidence of new onset postoperative atrial fibrillation in patients undergoing cardiac surgery.

CHAPTER 3: METHODS

Overview

This chapter will start with a description of the methodology for the derivation of a clinical prediction or decision rule. Following this section, the methodological details of the study regarding predictor variables, data extraction, modeling and internal validation will be reported.

3.1 Methodological Standards for Decision Rules

This project will follow this method up to the point of internal validation. The descriptions of external validation, implementation, economic analysis and dissemination are included for completeness and will be the long-term goal of this project. A decision rule is an evidence based analysis created to help clinicians make an educated management plan. The rule can indicate treatment and be called a decision rule, or predict an outcome and be labelled a prediction rule which is the case for this study. Standards for the development of prediction rules from the stages of inception through to implementation have been published in order to facilitate quality appraisal of research being published (Laupacis, Sekar, and Stiell 1997, Stiell and Wells 1999, McGinn et al. 2000, Wasson et al. 1985). The development of a decision rule should go through six stages: identification, derivation, validation, implementation, economic analysis and dissemination.

3.1.1 Identification

When framing the basis for clinical need, the rule should address a condition that is commonly encountered to facilitate general use. There should be variation in clinical practice with no established standard of care. A rule derived for a rare condition would have limited use.

3.1.2 Derivation

This stage consists of collecting information in a cohort of individuals with unbiased prospective identification of the outcome of interest. All important predictor variables must be identified and collected without knowledge of the outcome of interest. The definition of the outcome and all important predictor variables should be clearly outlined ahead of time. Predictor variables for consideration must also be obtainable across different scopes of practice and preferably be an objective measure to ensure reproducibility. The sample size and inclusion/exclusion criteria should be well described. Factors to consider in determination of sample size are the number of predictor variables to be included and the desired level of accuracy for the rule. It is generally acceptable to have at least ten outcomes per predictor variable included in the model (Shapiro 2006). The desired clinical sensitivity drives the targeted sensitivity of the rule as well as the lower end of the 95% confidence limits. The targeted sensitivity and the incidence of the outcome of interest will dictate the sample size requirement for derivation. The mathematical techniques used for prediction rule derivation initially involve a screening of predictor variables using univariate analyses and then multivariable analyses using logistic and/or recursive partitioning. The final prediction rule should make clinical sense and be easy to use with minimal calculations and components to facilitate implementation.

3.1.3 Validation

The newly derived prediction rule needs to demonstrate its generalizability in different medical centers of varying clinical practice. The rule's accuracy should be prospectively validated internally and externally in different cohorts, thereby moving the rule up the hierarchy of evidence (Levels 4 to 1) for clinical prediction rules. Internal validation can comprise of

implementation of the prediction rule in a subset of the same cohort using methods such as bootstrapping (Level 4) or prospective validation in the same center where the rule was derived (Level 3) with a different cohort. The accuracy of the rule then needs to be further tested in multiple centers distinct from the derivation center (Level 2). Validation in large multiple centers with impact assessment would move the prediction rule to Level 1, the highest level of evidence (McGinn et al. 2000). During these steps of validation, the ease of use and sensibility of the rule should be assessed by surveying the physicians who are applying the rules.

3.1.4 Implementation

Integration of the prediction rule into clinical practice would then assess the impact and level of acceptance of the rule. Acceptance into practice is dependent on the outcome involved and the magnitude of risk with a false negative. Severe consequences require that the rule have a sensitivity of 100%, otherwise the clinician may not be inclined to use the rule. Such an example would be the CATCH decision rule for when to use computed tomography in children with suspected minor head injuries. A clinician would never use the rule if there was any chance of missing a serious finding and as such the investigators set the sensitivity at 100% (Osmond et al. 2010). The aim of a prediction rule would be to produce a positive change in practice be it lower resource use, shorter waiting times, less complications etc. all of which can be included in an impact analysis.

3.1.5 Economic analysis

In a health care system of limited resources, cost-effectiveness can be a driving force towards implementation of these evidence based instruments. This can be part of the impact analysis especially if the rule involves an intervention or diagnostic test (Anis et al 1995). Rules

that improve safety can lead to cost savings by avoiding expenditures associated with complications.

3.1.6 Dissemination

This is often the highest and longest standing barrier to all new scientific knowledge. Dissemination strategies usually involve a multi-disciplinary approach between experts in knowledge transfer, educators, clinicians and allied health professionals (Gaddis et al 2007).

3.2 Study

3.2.1 Study Design

This study is a retrospective cohort study using prospectively collected data from the Perioperative Database Unit at the University of Ottawa Heart Institute and collated with supplemental data obtained from focused chart reviews.

3.2.2 Institutional Database Description

The University of Ottawa Heart Institute has a Perioperative Database Unit that is comprised of three distinct databases covering differing perioperative periods. The Unit prospectively collects hundreds of variables on all patients undergoing cardiac surgery. The three databases are the Perioperative Cardiac Anesthesia Database, the Cardiac Surgery Intensive Care Unit Database and the Cardiac Surgery Database. All data are collected for quality assurance and to monitor institutional outcome measures. Every patient seen at the University of Ottawa Heart Institute is asked to sign a consent form for chart review and consideration for recruitment into research studies. Any proposed research performed using this institutional database requires ethics board approval for chart review.

The infrastructure for those databases is supported by the divisions of Cardiac Anesthesiology and Cardiac Surgery. The Perioperative Cardiac Anesthesia Database contains information relevant to the preoperative and intraoperative periods. Information regarding the patient after the surgery is then collected in the Cardiac Surgery Intensive Care Unit Database until discharge onto the ward. The Cardiac Surgery Database contains variables that span from the time of surgery to the time of discharge from hospital. The standardized data collection sheets are provided in Appendix A, B and C. Datasheet collection, chart reviewing and database entry are performed daily by four independent dedicated research assistants, who have substitutes during times of absence. Quality control and audits are performed regularly by the database unit chairman. Although the data is not stored in the same database, the database managers have access to all and can collate requested information after ethics board approval. The patient's hospital number and date of surgery were used to link the three databases for this study.

3.2.3 Study Population

All patients undergoing eligible cardiac surgery procedures at the University of Ottawa Heart Institute from January 1 2010 until December 31 2010 were screened for inclusion in the study.

3.2.3.1 Inclusion criteria

1. Patients having elective or urgent cardiac surgery procedures that include: coronary artery bypass grafting, valve surgery or a combination of bypass grafting and valve surgery. In order to improve the generalizability of the decision rule, the study population was

restricted to these procedures because they by in large constitute the majority of procedures performed in all cardiac surgery centers.

3.2.3.3 Exclusion criteria:

1. Patients less than 18 years old.
2. Patients with any history of atrial fibrillation preoperatively. The original exclusion was preoperative diagnosis of atrial fibrillation and undergoing treatment (rate or rhythm control, anticoagulation). However, this definition missed three sets of patients who had atrial fibrillation, namely: a) patients recently diagnosed with atrial fibrillation but not started on anticoagulation because of the imminent prospect of surgery; b) patients with contraindications to anticoagulation or medications; and c) patients dependent on a pacemaker but have atrial fibrillation as their underlying rhythm. Due to the high event rate (30.5% incidence of the outcome), we chose to eliminate all patients with any history of atrial fibrillation including those with intermittent atrial fibrillation not on treatment and admitted with atrial fibrillation due to acute physiological stresses (such as heart failure, exacerbation of chronic obstruction pulmonary disease, acute papillary muscle rupture of the mitral valve, sepsis etc.).
3. Patients undergoing the following procedures: heart transplantation, pulmonary thromboendarterectomy, isolated aortic arch procedures, ventricular assist device insertion, extracorporeal membrane oxygenation insertion, percutaneous aortic valve replacement. These procedures involve very acutely ill patients undergoing complicated procedures specific to only a few large cardiac surgical centers in Canada and would limit the generalizability of the prediction rule.

4. Patients having surgical ablation of atrial fibrillation included in their surgical procedure. Inclusion of this procedure in their surgical agenda would suggest that the patient has a history of preoperative atrial fibrillation necessitating treatment.

3.2.4 Data Collection

3.2.4.1 Predictor Variable Selection

An exhaustive list of 32 clinical predictor variables for the development of postoperative atrial fibrillation was compiled from the published literature by the principal investigator. A consensus meeting of five physician experts consisting of members from the Divisions of Cardiac Surgery, Cardiac Anesthesiology and Cardiac Surgery Intensive Care Unit convened to shorten this list to those of clinical importance for abstraction from the databases and chart reviews. Table 2 lists the final 28 predictors variables that the group decided to include in the decision rule derivation.

Table 2

Clinical Predictor Variables Collected and Definitions (* values extracted directly from database)

Variable Number	Variable Name	Definition
1*	gender	
2*	age	years
3*	coronary artery disease	greater than 50% stenosis in a major coronary artery
4	left atrial size	description or measurement in millimeters on preoperative echocardiogram (includes in procedure before cardiopulmonary bypass)
5	obesity	where BMI≥30; calculated body mass index= weight(kg)/height(m)^2
6*	congestive heart failure	severity graded by New York Heart Association classes 1-4 performed on preoperative assessment
7*	diabetes mellitus	previously diagnosed on diet or medications or fasting glucose ≥7.0 mmol/L
8*	hypothyroidism	on medication
9*	stroke	neurologic deficit lasting >24hours ; ischemic or embolic in origin
10*	hypertension	(systolic blood pressure>140 mm Hg and or diastolic blood pressure>90 mm Hg or controlled on medication)

11	renal failure	preoperative creatinine clearance<60ml/hr calculated: Crockcroft equation: (140-age(yrs))*weight(kg)/ serum creatinine(μmol/L)*0.8136
12*	smoking history	never, current, remote (stopped >1 year ago)
13*	chronic obstructive pulmonary disease	diagnosis from history and using regular puffers or systemic steroids
14	beta-blocker	preoperative medication
15	statin	preoperative medication
16	calcium channel blocker	preoperative medication
17	digoxin	preoperative medication
18	steroids	preoperative medication – oral or intravenous route
19	left ventricular function	ejection fraction classified according to American Society of Echocardiography recommendations
20	right ventricular function	as reported in the preoperative echocardiogram
21	mitral valve disease	mitral regurgitation grade 1-4 or mitral stenosis mild-severe
22	myocardial infarction within 7 days of surgery	
23*	repeat cardiac surgery	
24*	surgical procedure	coronary artery bypass graft, valve surgery or combination
25*	cardiopulmonary bypass	procedure performed on or off cardiopulmonary bypass
26*	urgency	elective or urgent
27*	valve undergoing surgery	tricuspid, pulmonic, mitral, aortic
28*	CARE score	Cardiac Anesthesia Risk Evaluation score – tool evaluating risk of perioperative morbidity and mortality

3.2.4.2 Ethical Concerns.

Written application for data extraction from the Perioperative Database Unit was approved (see Appendix F), followed by approval from the Ethics Review Board of the University of Ottawa Heart Institute for expedited chart review (see Appendix G). As this study involves retrospective chart review with no patient contact, it was deemed unnecessary to obtain consent for this study. Datasheets containing necessary patient identifiers for chart review were all sent to the reviewers via secure in hospital email system and all chart reviews were performed in hospital. After all chart reviews and data were compiled, all patient identifiers (name, hospital identification number, birthday and date of procedure) were

removed from the datasheet and replaced by a study number. Only the principal investigator (thesis candidate) had access to the master list linking study number to chart identification.

3.2.4.3 Abstraction from Databases

An inquiry into the databases was made to include all the variables in Tables 2 marked by an asterisk. Both hospital chart number and date of surgery were used to identify patients. When patients have more than one procedure in one year, the data from the first procedure was used. Data verification by chart review, supplementing missing laboratory values, calculations of body mass index, renal function and dataset cleaning was performed by the author. Cases were eliminated based on the inclusion and exclusion criteria as much as possible before further chart review. A subset of the dataset was prepared for the chart reviewers to minimize accidental changes.

3.2.4.4 Definition of Outcome Measure

3.2.4.4.1 Outcome Definition

New onset postoperative atrial fibrillation (POAF) was defined as an irregularly irregular heart rhythm (as recorded on electrocardiogram or on telemetry monitoring) requiring treatment after surgery any time during the hospital stay, in patients without previous history of atrial fibrillation. Treatment can entail oral or intravenous amiodarone or electrical cardioversion in the intensive care unit, in addition to escalation of beta-blockers or addition of medications on the ward for heart rate or rhythm control.

3.2.4.4.2 Ascertainment of Outcome

New onset POAF was captured using three different data points from the three source databases. The Cardiac Anesthesia Database has a field for preoperative atrial fibrillation defined as an irregularly irregular heart rhythm any time before surgery regardless of whether they were receiving treatment. Postoperative atrial fibrillation is collected in both the Cardiac Surgery Intensive Care Unit Database and the Cardiac Surgery Database by two separate teams. The Cardiac Surgery Intensive Care Unit Database documents anyone with postoperative atrial fibrillation (POAF) defined as an irregularly irregular heart rhythm requiring treatment (cardioversion or medications for rhythm control) in the intensive care unit (ICU). The definition of new postoperative atrial fibrillation in the Cardiac Surgery Database includes patients who were not on previous treatment, requiring treatment before discharge from hospital. Data from the Cardiac Surgery Intensive Care Unit Database and Cardiac Surgery Database were corroborated to ensure no events were missed. No information on the time from surgery to the development of atrial fibrillation was available in the database.

3.2.4.5 Chart Review

In order to avoid misclassification of the outcome measure, every individual enrolled in the study had either an abbreviated or thorough chart review depending on the presence of atrial fibrillation in their medical history or course in hospital. The charts of patients without any perioperative atrial fibrillation had an abbreviated chart review consisting of 16 data points performed by one of eight different reviewers. The reviewers were seven physicians and one research nurse. All reviewers were given written instructions and definitions for data abstraction into an electronic database (see Appendix D). Of note, each reviewer was asked to

confirm the presence or absence of the outcome of interest. Any new events discovered were forwarded to the principal investigator for thorough chart review. The charts of patients with any preoperative or perioperative atrial fibrillation were all reviewed by the principal investigator. In this manner all patients with any preoperative history of atrial fibrillation were excluded from the study. Every patient who developed new onset postoperative atrial fibrillation had their chart reviewed to collect data with regards to course in hospital, complications, length of stay and postoperative follow-up to as recent as June 2012 wherever data is available. These variables included:

1. Complications related to atrial fibrillation: readmission to the intensive care unit, congestive heart failure , cardiac arrest, rhythm causes hemodynamic instability or is refractory to medications requiring electrical cardioversion, bleeding, ischemic or hemorrhagic stroke;
2. length of stay in hospital (in days);
3. rhythm on discharge from hospital;
4. discharge medications pertinent to heart rhythm and rate control and anticoagulation;
5. destination after discharge from hospital (i.e. home, convalescent care, other hospital);
6. heart rhythm on first postoperative visit;
7. number of days post-discharge of first postoperative visit;
8. readmission to any hospital within 6 months of discharge;
9. cause for readmission and events during in hospital stay;
10. cardioversion as an outpatient;

11. clinically important medical events since heart surgery (i.e. postoperative myocardial infarction, presentation to the emergency department, gastrointestinal bleeds, strokes etc.);
12. most recent documented heart rhythm;
13. survival.

3.2.4.6 Quality Assurance

The chart reviews were performed by eight individuals. The short chart reviews had 16 data points each and the longer chart reviews had 26 data points. At least 5% of each reviewer's set of charts were independently audited by a second reviewer. Reviewers 2-8 were audited by reviewer 1. Reviewer 1's full extensive chart reviews were audited by reviewer 2. The concordance was reported as a quotient of the agree/total data points.

3.2.5 Sample Size Calculation

The sample size calculation was based on the desired sensitivity of the prediction rule. This is a clinically driven threshold based on clinician judgement gained from working in that field of specialty. An informal survey of the physicians working in the intensive care unit helped the investigators choose a target sensitivity of at least 80% with the highest attainable specificity. From previous studies at our institution, the incidence of postoperative atrial fibrillation (POAF) was between 11.1% (incidence in cardiac surgery intensive care unit) and 29.6% (in-hospital incidence in patients with single or combined aortic valve surgery). The incidence in the cardiac intensive care unit was recognized as a gross underestimation of the true incidence because most patients only stay one or two days in the unit before discharged to the ward, while the peak incidence of occurrence of atrial fibrillation was on postoperative day three. The

average of the two figures would give a conservative estimate of 20% incidence of new onset POAF. Drawing from previous work done in our institution, the average number of procedures eligible for inclusion in this study would be 1200 cases per year, giving a predicted 240 cases per year of new onset postoperative atrial fibrillation (Tran et al 2012). Sensitivity confidence intervals calculations were performed with the online calculator: http://faculty.vassar.edu/lowry/clin1.html which used the method described by Newcombe (Newcombe 1998). Since the exact incidence of postoperative new onset atrial fibrillation was unknown, we planned to collect 10 outcomes per predictor variable considered, starting with the most recent year, 2010 and going backwards in time. The lower bound of the 95% confidence interval for sensitivity will be targeted at 80%. For 28 predictor variables we would need 280 outcome events and if one assumes a very conservative 20% incidence, a total of 1680 chart reviews covering a 14 month period. If the target sensitivity of the decision rule for this population was 86%, then the 95% confidence interval would be 80 to 90%. Our plan was to start abstracting charts in the calendar year 2010 and adjust our period depending on the event rate to achieve 280 outcomes.

3.2.6 Data Analysis

3.2.6.1 Database management

Database management was performed by the principal investigator using Microsoft Excel 2007. Completeness of data was verified and all missing data was abstracted directly from the hospital health records as much as possible. The spreadsheet was exported into Statistical Analysis Software (SAS) 9.2 for analyses except for recursive partitioning which was done using KnowledgeSEEKER 7.6 (Angoss Toronto Canada 2012). All multi-level categorical variables were

dichotomized where possible, if not they were simplified to clinically important levels. For example instead of having 5 categories for heart failure (normal and all four classes of the New York Heart Association heart failure (NYHA) classification), the variable was instead collapsed into three categories: normal, mild (NYHA1-2) and severe (NYHA3-4). This approach is in keeping with our aim to make a simple prediction rule; the chosen categories are closer to clinical impressions of disease severity. The same was done with the different grades of valvular regurgitation, most clinicians do not know the difference between 1+ versus 3+ mitral regurgitation, but they understand normal versus mild versus moderate-severe. The principal investigator is qualified to make these decisions because she is a practicing specialist in Cardiac Anesthesiology with certification from the National Board of Echocardiography in Advanced Perioperative Transesophageal Echocardiography. All variable definitions are provided in Appendix E.

3.2.6.2 Descriptive Statistics

This section was divided into: 1) descriptive statistics for the entire study cohort as it pertained to the baseline characteristics and predictor variables for prediction rule derivation 2) descriptive statistics comparing those who did and not develop the outcome during the perioperative stay in hospital and 3) description of results obtained from the chart review for the subset of patients who developed new onset postoperative. Continuous variables were reported with the range as well as mean and standard deviations. Categorical variables were presented in proportions and assessed for outliers by frequency tables and manual checks.

3.2.6.3 Univariate Analyses

For the purposes of prediction rule derivation univariate analyses were performed to test the association of each predictor variable with new onset postoperative atrial fibrillation. The Pearson Chi-Square test or Fisher's exact test when the observations were less than five was used for categorical data and the independent t-test for continuous data. In order to dichotomize age, the relationship between the variable age with the outcome was assessed at increments of 5 years from 60 to above 80 years to identify an age cut. Because 28 variables are too many to insert in the logistic model, a cut-off p-value < 0.2 from the univariate analysis was chosen for inclusion into the multivariable model and recursive partitioning. Morbid obesity was defined as per the World Health Organization definition with a body mass index of $\geq 30 kg/m^2$. The definition of renal failure was set at a calculated creatinine clearance of <60mL/min , the level corresponding to Stage 3 chronic kidney disease with moderate reduction in glomerular filtration rate as per the National Kidney Foundation guidelines. Left atrial dilatation was defined as a measured left atrial size by transthoracic echocardiography of >41mm as per our institutional standard.

For the purposes of describing the epidemiology of new onset postoperative atrial fibrillation, univariate analyses were performed to compare clinically significant outcomes between those who did and did not develop the outcome of interest. These variables include baseline characteristics and course in hospital. Again, the Pearson Chi-Square test or Fisher's exact test when the observations were less than five was used for categorical data and the independent t-test for continuous data. A cut-off p-value < 0.05 was considered statistically significant.

3.2.6.4 Prediction Rule Derivation

Because the etiology of postoperative atrial fibrillation is most likely multifactorial, it was only appropriate to use multivariable methods to derive the rule. Two methods were chosen for rule derivation: multivariable logistic regression and recursive partitioning. The target sensitivity for the prediction rule was a lower 95% confidence limit of 80% with the highest specificity possible.

3.2.6.4.1 Multivariable Logistic Regression

The logistic regression model was derived by step-wise forward selection with a p-value entry of 0.2 and two different p-values for removal: the statistically significant 0.05 and the conventional 0.15. Patients undergoing simple coronary artery bypass grafting with normal left ventricular systolic function found on angiogram do not routinely have preoperative echocardiograms. As a result, there was a small portion of data missing not a random: left ventricular function, right ventricular function and left atrial size. Sensitivity analyses were performed assuming both extremes (all normal and all abnormal) for the missing data and compared to the model with complete data only. Discrimination of the models was assessed by the c-statistic. Assessment of model fit was tested using the Hosmer-Lemeshow goodness-of-fit. The odds ratio with 95% confidence limits and the beta coefficients for all variables in the final model were reported.

In order to improve the ease of use of the prediction rule for the busy clinician, a risk score was derived by dividing all the beta coefficients of the variables in the final model by the smallest beta coefficient (Sullivan 2004). The values were rounded to the nearest whole number and a total risk score was calculated for each patient in the study. This risk score was

inserted into a logistic regression model with the original dataset to produce the probabilities of developing new onset postoperative atrial fibrillation for each score.

3.2.6.4.2 Recursive Partitioning

Classification and regression trees were used to perform recursive partitioning to isolate the predictors that would produce a prediction rule with the desired sensitivity and highest possible specificity. Only variables with a $p<0.2$ from the univariate analyses were entered into the software, which then performed Chi-squared analysis between the variables and the outcome to divide the patients into groups of high and low risk for developing the outcome. The decision rules produced by this method were then eliminated if their sensitivity didn't meet the lower limit cut-off of 80% for the 95% confidence interval. Considerations were then given to the variables within the rules, preferring those that were more clinically feasible. The remaining candidate rules then had their specificities compared and the model with the highest specificity was favored.

3.2.7 Classification Performance

The chosen decision rule was applied to the entire cohort and a comparison between the predicted status of each patient with their actual status, with regard to postoperative atrial fibrillation, was made. This produced an estimate of the specificity and sensitivity of the prediction rule with 95% confidence intervals.

3.2.8 Internal validation

A statistician from the University of Ottawa Heart Institute Research Methods Center was recruited to help with this part of the rule derivation. Bootstrapping is a resampling

technique from the derivation cohort used to estimate the predictive accuracy of the prediction rule. Bootstrapping of both the logistic regression model and the decision rule from recursive partitioning were performed. Five thousand bootstrap samples of equal size to the study population were selected with replacement. For the logistic regression model, the 5000 bootstraps produced 5000 estimates of the beta coefficients which were then averaged to give a mean and standard deviations. Similarly, the decision rule was performed 5000 times on sample sizes equals to the study population with replacement to produce 5000 estimates of sensitivity and specificity. The mean values with standard deviations were reported. Comparisons of the means from the two bootstrapping exercises were compared to that of their respective models; similar values would further support an appropriate fit for the models.

Chapter 4: Results

4.1 Quality Assurance

The results of the quality assurance audit are listed in Table 3. A large portion of the chart reviews were performed by two principal reviewers (72.3%). The average percentage agreement per reviewer was 96.0%. When there were disagreements in the datapoints, review of the electronic chart was performed by the author for the third time and corrections were made. Discrepancies usually involved omission of data by one reviewer, with the exception of one datapoint where the wrong ejection fraction was inserted.

Table 3
Chart Review Quality Assurance Audit

Reviewer	Number of Charts Reviewed	# of Charts Audited	Number of data points disagree	% agreement with auditor
1	604	34	30/884	96.6
2	200	10	6/160	96.2
3	51	3	1/48	97.9
4	50	3	2/48	95.8
5	50	3	4/48	91.7
6	50	3	2/48	95.8
7	50	3	1/48	97.9
8	50	3	2/48	95.8

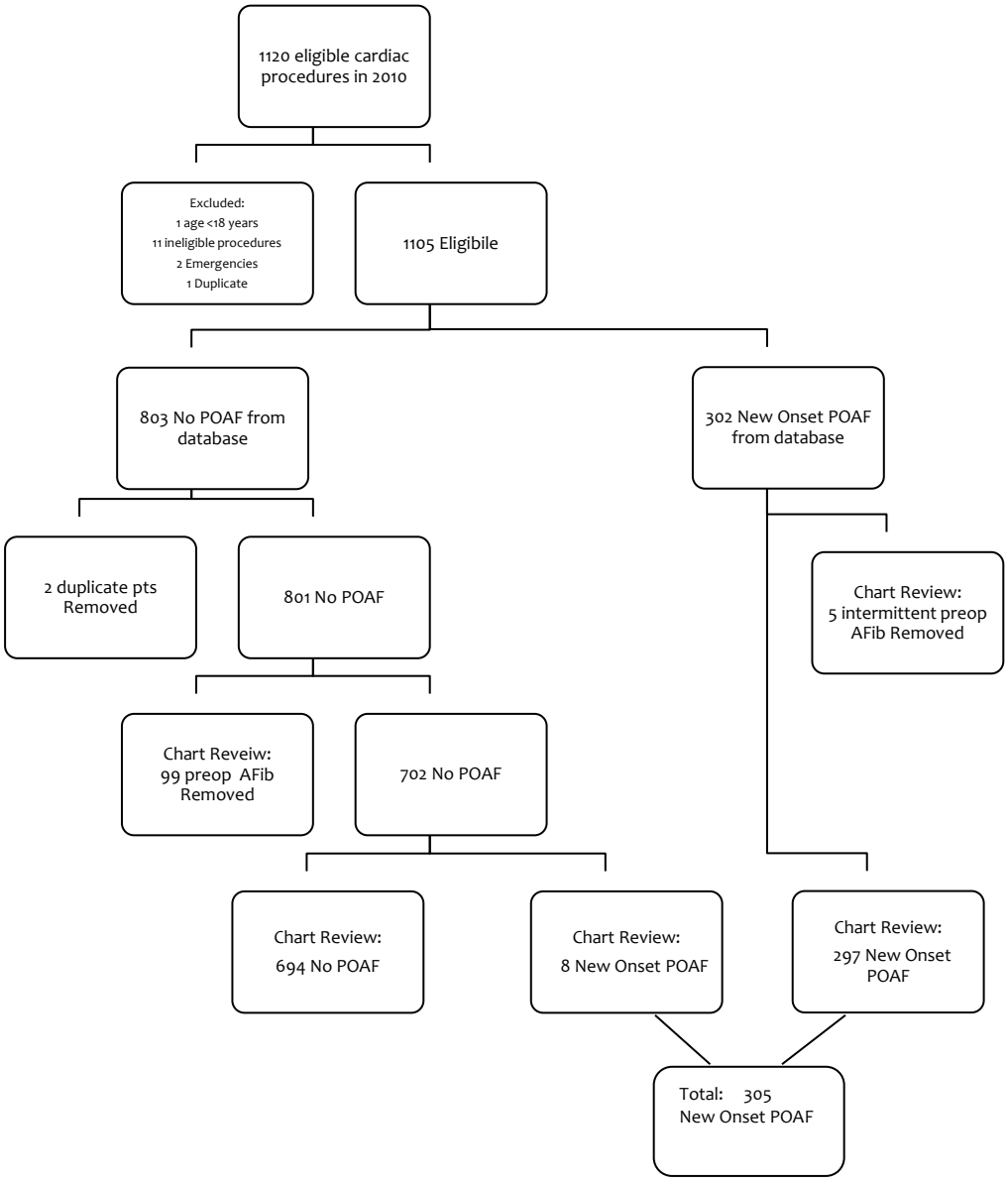
4.2 New Onset Atrial Fibrillation

The database query for eligible cardiac surgical procedures performed in the calendar year 2010 yielded 1120 patients of which 1105 met eligibility criteria. Figure 1 depicts the flow of the study population as the charts were reviewed and more patients were withdrawn from the study most often due to pre-existing atrial fibrillation. The final study size consisted of 999 patients with 305 cases of new onset atrial fibrillation. This 30.5% event rate was much higher

than the estimated 20% incidence of new onset postoperative atrial fibrillation producing an adequate sample size to meet the target sensitivity of 80%.

Figure 1

Flowchart for Patient Enrollment and Group Allocation



Preop: preoperative, POAF: postoperative atrial fibrillation, AFib: atrial fibrillation

4.2.1 Descriptive Statistics

Table 4 lists the baseline characteristics of the study cohort. The age of the study population ranged from 19 to 92 years with a mean of 64.8±11.9 (Table 5). More than half (54.0%) of the eligible patients were greater or equal to 65 years of age with a predominance of men (71.9%). Co-morbid diseases included obesity (36.8%), diabetes mellitus (30.3%) and renal failure (29.6%). The incidence of coronary artery disease was 75.4% and 57.4% of patients had valvular disease.

Table 4
Characteristics of Eligible Patients Undergoing Cardiac Surgery in 2010

Variable	**No. of patients (%) n=999**
Demographics	
Age ≥65 years	540(54.0)
Male	718(71.9)
Obese (BMI≥ 30 kg/m^2)	368(36.8)
Co-morbidities	
Hyperlipidemia	731(73.2)
Diabetes mellitus	303(30.3)
Renal failure (CrCl<60mL/min)	296(29.6)
COPD on puffers or systemic steroids	134(13.4)
Smoker (never/remote >1 year/current)	320(32.0)/421(42.1)/258(25.8)
Hypothyroidism	102(10.2)
Cardiovascular	
MI within 7 days of surgery	27 (2.7)
NYHA (0/mild/severe)	439(43.9)/317(3.2)/243(24.3)
Left ventricular function(normal/ mild/ moderate/severe)	706(70.9)/135(13.6)/115(11.6)/38(3.9)
Right ventricular function(normal/mild/ moderate/severe)	916(94.7)/28(3.3)/12(1.4)/5(0.6)
Left atrial dilatation (>41mm)	342(36.0)
Hypertension	747(74.8)
Coronary artery disease	753(75.4)
Valvular Disease	573(57.4)

Aortic stenosis	318(31.8)
Aortic regurgitation	230(23.0)
Mitral stenosis	19(1.9)
Mitral regurgitation	324(32.4)
Mitral valve disease(Normal/Mild/Severe)	620(62)/267(27)/112(11.2)
Pulmonary stenosis	2(0.2)
Pulmonary regurgitation	35(3.5)
Tricuspid stenosis	1(0.1)
Tricuspid regurgitation	175(17.5)
Preoperative Pharmacological Therapy	
Beta-blocker	618(62.9)
Calcium channel blocker	274(27.4)
Digoxin	8(0.8)
Statin	708(70.9)
Amiodarone	2(0.2)
Systemic steroids	23(2.3)
Surgical Details	
Repeat sternotomy	50(5)
Urgent surgery	270(27)
Surgery type (CABG/valve/combo)	530(53)/285(28.5)/184(18.4)
Mitral valve surgery	115(11.5)
Cardiopulmonary bypass	935(93.6)
Preoperative Risk	
CARE 1/2/3/4/5	79(7.9)/413(41.3)/399(39.9)/95(9.5)/13(1.3)

BMI= body mass index in kg/m^2; CrCl= Creatinine Clearance;COPD= chronic obstructive pulmonary disease; MI = myocardial infarction; NYHA= New York Heart Association class heart failure; CABG=coronary artery bypass grafting; CARE=Cardiac Anesthesia Risk Evaluation Score

Table 5
Summary of Continuous Variables for All Eligible Patients Undergoing Cardiac Surgery (n=999)

Variable	Range	Measurement (±SD)	Standard Error
Age (years)	19-92	64.8±11.9	0.38
BMI (kg/m^2)	12.4-49.8	28.63±5.6	0.17
Left atrial size (mm)*	19-62	41.0±6.9	0.27
CrCl(mL/min)	7.9-253	78.6±33.1	78.6

*Missing 342 values; BMI= body mass index in kg/m^2; CrCl=creatinine clearance

4.2.2 *Intraoperative Details*

The surgical procedures performed included 530 (53.0%) coronary artery bypass grafting, 285 (28.5%) valve surgeries and the remainder were combined procedures (bypass and valve) (Table 4). The length of procedures (from skin incision to closure) ranged from 90 to 735 minutes with a mean of 233.6±66.8.

Table 6
Summary of Intraoperative Continuous Variables for All Eligible Patients

Variable	Range	Total Cohort (±SD) (n=999)	Standard Error
Operation time (mins)	90-735	233.6±66.9	2.1
Cross clamp time (mins)	0-306	67.7±36.2	1.1
Cardiopulmonary bypass time (mins)	0-390	97.2±48.2	1.5

SD= standard deviation

4.2.3 *Course in Hospital*

Table 7 summarizes some clinical details that occurred during the postoperative course in hospital. The length of stay in hospital ranged from 3 to 159 days with a mean of 9.74±11.2.

Table 7
Summary of Complications in Hospital for All Eligible Patients (n=999)

Variable		No. of patients (% of 999 pts)
Cardiovascular		
	Heart block	19(1.9)
	Cardiac Arrest	9(0.9)
	Cardiac Ischemia	13(1.3)
	Lower Limb Ischemia	4(0.4)
	Cardiogenic pulmonary edema	47(4.7)
Respiratory		
	Tracheostomy	12(1.2)
	Pulmonary Embolus	3(0.3)
Ischemic Bowel		7(0.7)
Liver failure		12(1.2)
Renal		
	New onset acute renal failure	114(11.4)

	Renal Insufficiency	175(17.5)
	New requirement for dialysis	22(2.2)
Infection		41(4.1)
Readmit to ICU		17(1.7)
Neurological		
	Seizures	14(1.4)
	Strokes	23(2.3)
Bleeding		
	Hemothorax	5(0.5)
	Upper gastrointestinal bleed	12(1.2)
	Lower gastrointestinal bleed	6(0.6)
Deceased		9(0.9)

ICU= intensive care unit
[f] Fisher's exact test used, otherwise Pearson Chi-Square value used
Infection includes: ventilator associated pneumonia, urinary tract infections, deep sternal wound infections
New onset acute renal failure: If creatinine>150µmol/L in the postoperative period
Renal insufficiency: new creatinine elevation >150µmol/L or above baseline for those with chronic renal failure
Cerebral Vascular accident: both ischemic and hemorrhagic strokes

4.2.4 Post-discharge follow-up

To further delineate the natural course of new onset postoperative atrial fibrillation, the patients who had this outcome had all available records on The Ottawa Hospital electronic medical record reviewed from time of discharge until June 30th 2012. Of the 297 surviving patients who developed new onset atrial fibrillation, 247 (83.1%) patients had converted to sinus rhythm and only 34 (11.4%) remained in atrial fibrillation upon discharge from hospital. The remaining patients had a paced heart rate (3.4%) or atrial flutter (2.0%). Of note, 7 of the 10 paced patients had severe bradycardia requiring new pacemaker insertions after heart surgery. Information on discharge disposition and medications were missing in three patients. The majority of patients were discharged home (263, 89.5%) while 18(6.1%) were transferred to another hospital and 13 (4.4%) went to convalescent care. Table 8 summarizes the different medications prescribed to the patients. Despite having converted to sinus rhythm, 86 (35.0%) patients were still placed on blood thinners for a variety of reasons (low ejection fraction, valve

surgery, intermittent atrial fibrillation) and 70(28.4%) were prescribed an anti-arrhythmic agent, amiodarone, to keep their rhythm regular.

Table 8
Discharge Medications for Patients with New Onset Postoperative Atrial Fibrillation (n=295)

	Heart Rhythm at Time of Hospital Discharge			
	Atrial fibrillation (n=34)	Atrial flutter (n=6)	Sinus rhythm (n=247)	Permanent pacemaker (n=8)
Drugs				
Beta-blocker	32	6	236	6
Calcium channel blocker	2	0	16	1
Amiodarone	11	5	70	1
Digoxin	3	0	12	0
Coumadin	30	4	86	6

The first postoperative visit was usually performed within the first three months after discharge. Seventeen patients were lost in the follow-up. Table 9 summarizes the heart rhythm found on electrocardiogram at this first visit, listed according to what heart rhythm the patient was in upon discharge. More than half of the patients who left the hospital in atrial fibrillation converted to sinus (52.9%) whereas 4.5% of the patients who were in sinus rhythm reverted back

Table 9
Heart Rhythm on First Clinic Visit After Discharge for Patients with New Onset Postoperative Atrial Fibrillation (n=297)

	Heart Rhythm on First Clinic Visit					
	Atrial fibrillation (n=20)	Atrial flutter (n=6)	1 or 2nd degree heart block (n=4)	Sinus rhythm (n=233)	Paced (n=8)	Not available (n=26)
Rhythm on discharge						
Atrial fibrillation (n=34)	8	3	1	18	1	3
Atrial flutter (n=6)		1		3		2
Sinus (n=247)	11	2	3	209	1	21
Paced rhythm (n=10)	1			3	6	

to atrial fibrillation at the time of their first postoperative visit. Long-term follow-up affiliated with The Ottawa Hospital ranged from 9 days to 28 months with a mean of 14 ±7.6 months. Six patients died during the follow-up period. All deaths can potentially be related to the management of atrial fibrillation. Three cases were from subtherapeutic anticoagulation: one as early as 26 days after going home, from a massive cardioembolic stroke with an INR of 1.7 and two cases of mesenteric ischemia (blood flow obstruction to small bowel). The other causes of death were from bleeding; two cases of subdural hematomas and a retroperitoneal bleed.

4.3 Univariate Analysis

4.3.1 Selection of Predictor Variables for Rule Derivation

Table 10 summarizes the results of the univariate analyses with all the categorical predictor variables for prediction rule derivation. The table includes the different values for the 5 cut-off points for age. Only three variables had missing data: left ventricular function, right ventricular function and left atrial size. The groups to which the missing data-points belonged are denoted at the bottom of the table. The 19 variables meeting the criteria for inclusion into the multiple logistic regression model are marked with asterisks in the table. Predictor variables found to have a statistically significant association with new onset postoperative atrial fibrillation with a p-value of <0.05 were: age, renal failure, chronic obstructive pulmonary disease, hypothyroidism, New York Heart Association heart failure class, right ventricular function, left atrial dilatation, valvular disease, specifically mitral valve disease, preoperative digoxin use, surgery type, type of valve surgery, mitral valve surgery and the CARE score (Cardiac Anesthesia Risk Evaluation a validated tool used to predict morbidity and mortality after cardiac surgery).

Table 10
Univariate Analyses of Candidate Predictor Variables

Variable			POAF		p-value
			No (% of n=694)	Yes (% of n=305)	
Demographics					
	Age ≥60 years		451(65.0)	255(83.6)	<0.001*
	Age ≥65 years		325(46.8)	215(70.5)	<0.001*
	Age ≥70 years		211(30.4)	160(52.5)	<0.001*
	Age ≥75 years		121(17.4)	105(34.4)	<0.001*
	Age ≥80 years		48(6.9)	39(12.8)	0.002*
	Male		510(73.5)	208(68.2)	0.087*
	Obese (BMI ≥ 30kg/m^2)		262(37.8)	106(34.7)	0.366
Co-Morbidities					
	Diabetes mellitus		213(30.7)	90(29.5)	0.708
	Renal failure (CrCl<60mL/min)		184(26.5)	112(36.7)	0.001*
	COPD on puffers or systemic steroids		82(11.8)	52(17.1)	0.025*
	Smoker				0.191*
		Remote (≥1 yr) Current	293(42.2) 189(27.2)	128(42.0) 69(22.6)	
	Hypothyroidism		59(8.5)	43(14.1)	0.007*
Cardiovascular					
	Myocardial infarction within 7 days of surgery		18(2.6)	9(3.0)	0.749
	NYHA heart failure class				0.002*
		Mild (NYHA 1-2) Severe (NYHA 3-4)	224(32.3) 147(21.2)	93(30.5) 96(31.5)	
	Left ventricular function [α]				0.107*
		Normal Mild Moderate Severe	498(72.3) 95(13.8) 76(11.0) 20(2.9)	208(67.9) 40(13.1) 39(12.8) 18(5.9)	
	Right ventricular function[β]				0.005*
		Normal Mild Moderate Severe	639(96.0) 17(2.9) 7(1.2) 3(0.5)	277(93.4) 11(4.0) 5(1.8) 2(0.7)	
	Left atrial size[γ]		205(16.2)	138(26.4)	<0.001*
	Left atrial dilatation (>41mm)[δ]		168(16.8)	127(12.7)	<0.001*
	Hypertension		507(73.0)	240(78.7)	0.059*
	Coronary artery disease		530(76.4)	223(73.1)	0.272
	Valvular disease		367(52.9)	206(67.5)	<0.001*
	Mitral valve disease				<0.001*
		Mild Severe	161(23.2) 57(8.2)	106(34.8) 55(18.0)	
Preoperative Pharmacological Therapy					
	Beta-blocker		430(62.0)	188(61.6)	0.924

	Calcium channel blocker		189(27.2)	85(27.9)	0.836
	Digoxin		3(0.4)	5(1.6)	0.049*
	Statin		494(71.2)	214(70.1)	0.744
	Systemic steroids		15(2.2)	8(2.6)	0.654
Surgical Details					
	Surgery type				<0.001*
		CABG	399(57.5)	131(43.0)	
		Valve	184(26.5)	101(33.1)	
		Combo	111(16.0)	73(23.9)	
	CPB		643(92.7)	292(95.7)	0.067*
	Valve type				<0.001*
		Aortic	216(31.1)	118(38.7)	
		Mitral	52(7.5)	42(13.8)	
		Tricuspid	5(0.7)	0	
		Pulmonary	1(0.1)	0	
		Combo	12(1.7)	11(3.6)	
	Mitral valve surgery		62(8.9)	53(17.8)	0.001*
	Repeat cardiac surgery		32(4.6)	18(5.9)	0.389
	Urgent surgery		182(26.2)	88(28.9)	0.389
	CARE Score				<0.001*
		1	68(9.8)	11(3.6)	
		2	300(43.2)	113(37.1)	
		3	270(38.9)	129(42.3)	
		4	52(7.5)	43(14.1)	
		5	4(0.6)	9(3.0)	

BMI= body mass index in kg/m^2;CrCl=creatinine clearance; COPD=chronic obstructive pulmonary disease; NYHA=New York Heart Association; CPB=cardiopulmonary bypass; CARE=cardiac anesthesia risk evaluation; CABG=coronary artery bypass grafting

*****p<0.2 cut-off, variable inserted into multiple logistic regression model

$^{\alpha}$ missing 5 values in POAF=N

$^{\beta}$ missing 20 values in POAF=N and 10 in POAF=Y

$^{\gamma}$ missing 39 values in POAF=N and 10 in POAF=Y

δ missing 255 values in POAF=N and 77 in POAF=Y, variable not used, please see results section

4.3.2 Comparing the Patients With and Without New Onset Postoperative Atrial Fibrillation

Univariate analyses comparing the categorical data between the two cohorts of patients have already been reported in the previous section. This section reports the univariate analyses for the four preoperative continuous variables. Consistent with the univariate analyses in the previous section, patients who developed new onset POAF were significantly older by 5.9 years and had a lower creatinine clearance by an average of 10mL/min. No difference was seen with

body mass index and although left atrial size is significantly larger in the patients who develop atrial fibrillation, the comparison is not valid with more than 30% missing data.

Table 11
Comparisons of Preoperative Variables Between Patients with and without New Onset Postoperative Atrial Fibrillation, by Univariate Analyses

Variable	Range	No POAF (±SD) (n=694)	POAF (±SD) (n=305)	p-value	95% CI of difference in Mean
Age (years)	19-92	63±12	68.9±10.3	<0.001	4.4-7.5
BMI (kg/m^2)	12.4-49.8	28.7±5.6	28.5±5.6	0.58	-0.97-0.54
Left atrial size (mm)*	19-62	40.2±6.8	42.6±6.8	<0.001	1.3-3.5
CrCl(mL/min)	7.9-253	81.7±34.2	71.4±29.6	<0.001	14.7-5.9

*Missing 332 values; BMI= body mass index in kg/m^2; CrCl=creatinine clearance; POAF=postoperative atrial fibrillation

The procedural times were marginally longer for patient who developed new onset postoperative atrial fibrillation 238.7±67 vs 231±67 minutes, p=0.058 (Table 12). Time spent on cardiopulmonary bypass was significantly longer, 102±46.5 vs 95.0±48.8 minutes, p=0.031.

Table 12
Comparisons of Intraoperative Variables Between Patients with and without New Onset Postoperative Atrial Fibrillation, by Univariate Analyses

Variable	Range	Total Cohort (±SD) (n=999)	Standard Error	No POAF (±SD) (n=694)	POAF (±SD) (n=305)	p-value	95% CI of difference in Mean
Operation time (mins)	90-735	233.6±66.9	2.1	231±66.6	239.7±66.9	0.058	-0.3-17.6
Cross clamp time (mins)	0-306	67.7±36.2	1.1	66.6±36.7	72.4±34.7	0.007	1.8-11.6
Cardiopulmonary bypass time (mins)	0-390	97.2±48.2	1.5	95.0±48.8	102.2±46.5	0.031	0.7-13.6

POAF= postoperative atrial fibrillation; SD= standard deviation

Those patients who developed new onset postoperative atrial fibrillation had a significantly longer length of stay in hospital (13.6 vs 8.1 days, p<0.001) compared to those who did not.

Table 13
Comparisons of Postoperative Complications Between Patients with and without Postoperative Atrial Fibrillation, by Univariate Analyses

Variable		Patients without POAF (% of 694 pts)	Patients with POAF (% of 305 pts)	p-value	Odds Ratio (95% CI)
Cardiovascular					
	Heart block	7(1.0)	12(3.9)	0.002	4.0(1.6-10.3)
	Cardiac Arrest	2(0.3)	7(2.3)	0.005[f]	8.3(1.7-39.4)
	Cardiac Ischemia	8(1.1)	5(1.6)	0.532	1.4(0.5-4.4)
	Lower Limb Ischemia	2(0.3)	2(0.7)	0.358[f]	2.3(0.3-16.3)
	Cardiogenic pulmonary edema	19(2.7)	28(9.2)	<0.001	3.6(2.0-6.5)
Respiratory					
	Tracheostomy	1(0.1)	11(3.6)	<0.001[f]	25.9(3.3-201.7)
	Pulmonary Embolus	2(0.3)	1(0.3)	0.665[f]	1.1(0.1-12.6)
Ischemic Bowel		2(0.3)	5(1.6)	0.031[f]	5.7(1.1-29.9)
Liver failure		5(0.7)	7(2.3)	0.035	3.3(1.0-10.3)
Renal					
	New onset acute renal failure	64(9.2)	50(16.4)	0.01	1.9(1.3-2.9)
	Renal Insufficiency	95(13.7)	80(26.2)	<0.001	2.2(1.6-3.1)
	New requirement for dialysis	7(1.0)	15(4.9)	<0.001	5.1(2.1-12.6)
Infection		14(2.0)	27(8.9)	<0.001	4.7(2.4-9.1)
Readmit to ICU		6(0.9)	11(3.6)	0.002	4.3(1.6-11.7)
Neurological					
	Seizures	10(1.4)	4(1.3)	0.873	0.9(0.3-2.9)
	Strokes	16(2.3)	7(2.3)	0.992	1.0(0.4-2.4)
Bleeding					
	Hemothorax	3(0.4)	2(0.7)	0.644[f]	1.5(0.3-9.1)
	Upper gastrointestinal bleed	4(0.6)	8(2.6)	0.006	4.6(1.4-15.5)
	Lower gastrointestinal bleed	1(0.1)	5(1.6)	0.012[f]	11.6(1.3-99.3)
Deceased		1(0.1)	8(2.6)	<0.001[f]	18.7(2.3-149.9)

POAF = new onset postoperative atrial fibrillation; ICU= intensive care unit
[f] Fisher's exact test used, otherwise Pearson Chi-Square value used
Infection includes: ventilator associated pneumonia, urinary tract infections, deep sternal wound infections
New onset acute renal failure: If creatinine>150µmol/L in the postoperative period
Renal insufficiency: new creatinine elevation >150µmol/L or above baseline for those with chronic renal failure
Cerebral Vascular accident: both ischemic and hemorrhagic strokes

The development of postoperative atrial fibrillation was associated with a significantly increased incidence of complications affecting morbidity and mortality in hospital (Table 13). Cardiovascular complications included severely diminished atrioventricular conduction, otherwise known as heart block (1.0% versus 3.9% of those with postoperative atrial fibrillation p=0.002), cardiac arrest (0.3% versus 2.3% p=0.005) and pulmonary edema secondary to heart failure (2.7% versus 9.2%, p<0.001). Patients who developed postoperative atrial fibrillation were also at increased risk for complications involving other organ systems with a significantly higher odds of developing ischemic bowel (OR 5.7, 95%CI 1.1-29.9), liver failure (OR 3.3, 95% CI 1.0-10.3), new onset acute renal failure (OR 1.9, 95%CI 1.3-2.9). Multi-organ failure often includes respiratory failure requiring a tracheostomy; this occurred more often in patients with postoperative atrial fibrillation (0.1% vs 3.6 % p<0.001) after a prolonged stay in the intensive care unit.

As previously mentioned, atrial fibrillation management involves the initiation of anticoagulation therapy to decrease the risk of embolic strokes which is balanced with the risk of bleeding (i.e. cerebral, surgical site, gastrointestinal tract). There was no difference in the number of strokes (2.3% in both groups) nor intra-thoracic blood collections known as hemothoraces (0.4 versus 0.7%, p=0.644) between the two groups. The database does not differentiate between strokes of embolic or hemorrhagic origin. However, there was a greater rate of gastrointestinal bleeds in the group with postoperative atrial fibrillation. The odds of developing a significant upper (OR 4.6, 95%CI 1.4-5.5) or lower (OR 11.6, 95%CI 1.3-99.2) gastrointestinal bleeding was higher in the patients with new onset postoperative atrial fibrillation.

The increased number of complications in the patients with new onset postoperative atrial fibrillation also resulted in a significantly higher odds of readmission to the intensive care unit (OR 4.3, 95%CI 1.6-11.7). There were eighteen readmissions (11 with postoperative atrial fibrillation and 6 without). The reasons for readmission in the group with the outcome of interest included septic shock, ventricular tachycardia, circulatory arrest secondary to hypoglycemia, two cases of high rate atrial fibrillation causing hemodynamic instability, three respiratory failures and three cases of gastrointestinal bleeds. Of note, two patients with the outcome of interest had two readmissions to the ICU which were not double counted. Those who did not have new onset atrial fibrillation were readmitted for sepsis, respiratory failure, delayed cardiac tamponade and three cases of gastrointestinal bleeds. The end result of the higher rate of adverse outcomes in the patients with new onset postoperative atrial fibrillation was an in-hospital mortality incidence of 2.6% compared to 0.1%, p-value <0.001.

4.4 Multivariable Logistic Regression

4.4.1 Initial Logistic Regression Model Derivation

Nineteen predictor variables were inserted into the model using multivariable logistic regression with stepwise elimination. All five age variables (with varying age cut-offs) were alternatively inserted in to the logistic regression model to find the age cut-off that best fit the model (Table 11). Models 1-5 included the CARE score (Cardiac Anesthesia Risk Evaluation) with varying ages whereas models 6-10 did not have the CARE score inserted into the model derivations. After the first five iterations of the model, the decision was made to exclude the CARE score from the model development. Although the score was highly associated with the outcome, p<0.001; the inclusion of a score embedding in the final prediction rule would make it

too complicated for the clinician to use. The c-statistic was highest in models 2 and 7 at 0.698 and 0.679, respectively; both of these models indicated that age ≥ 65 years would be the most appropriate cut-off to choose for the final model.

Table 14
Initial Multivariable Models Predicting New Onset Postoperative Atrial Fibrillation

Model No.	Variables	C-statistic (95%CI)	Hosmer-Lemeshow p-value	Chi-Square	Degrees of Freedom
1	Age ≥ 60 years, CARE score, mitral valve disease, left atrial dilatation	0.690 (0.654-0.726	0.6088	5.4305	7
2	Age ≥ 65 years, CARE score, mitral valve disease, left atrial dilatation	0.698 (0.661-0.734)	0.6316	6.1395	8
3	Age ≥ 70 years, CARE score, mitral valve disease, left atrial dilatation	0.684 (0.646-0.722)	0.7733	4.0564	7
4	Age ≥ 75 years, CARE score, mitral valve disease, left atrial dilatation	0.674 (0.636-0.712)	0.8157	3.6808	7
5	CARE score, mitral valve disease, left atrial dilatation, hypothyroidism	0.653 (0.615-0.691)	0.9880	1.3159	7
6	Age ≥ 60 years, mitral valve disease, left atrial dilatation	0.671 (0.635-0.707)	0.9457	1.192	5
7	Age ≥ 65 years, mitral valve disease, left atrial dilatation	0.679 (0.642-0.716)	0.9552	1.0877	5
8	Age ≥ 70 years, mitral valve disease, left atrial dilatation	0.666 (0.628-0.703)	0.9615	1.0125	5
9	Age ≥ 75 years, mitral valve disease, left atrial dilatation	0.657 (0.620-0.695)	0.9083	1.5412	5
10	Mitral valve disease, left atrial dilatation, renal failure, hypothyroidism	0.644 (0.606-0.681)	0.9683	0.9257	5

CARE=Cardiac Anesthesia Risk Evaluation; CI=confidence interval

Most of the development towards the final model revolved around the definition of the variable 'left atrial dilatation'. Initially model derivation used the variable left atrial size >41mm as the definition for dilatation, however there were 342 missing datapoints, as noted in Table 5. This large portion of missing data stems from three factors: 1) Not every patient had a pre-procedural echocardiogram; 2) an echocardiographer doesn't always report exact left atrial size, but more often uses descriptors of size instead (i.e., normal, mild, moderate or severely enlarged); and 3) left atrial size measurement is not valid using transesophageal

echocardiography (TEE). This last factor eliminates all patients who had TEEs performed in the operating room just before the surgery was performed. This large amount of missing data became important when multiple logistic regression predicting new onset postoperative atrial fibrillation revealed only five possible variables in the model: age, CARE score, mitral valve disease, hypothyroidism and left atrial size.

The model fit was only fair and varied a bit depending on which age cut-off was used, the results of which are summarized in Table 14. In attempt to improve model fit, a new variable called 'left atrial size' was created with four categories: normal, mild, moderate and severe. Since the original chart reviews only extracted left atrial size measurements, a thorough re-examination of all available echocardiogram reports was performed by the principal investigator. The new data points extracted were descriptors of left atrial size as well as reconfirmation of the mitral valve disease. Left atrial size was then collapsed into two categories: normal and dilated (incorporated all categories mild to severe). This decreased our missing left atrial sizes down to 49 missing values. Mitral valve disease was collapsed to clinically important categories of normal, mild (1-2+ mitral regurgitation) and moderate-to-severe disease (3-4+ mitral regurgitation).

4.4.2 Refining the Logistic Regression Model

With this updated dataset, 22 predictor variables (CARE score withdrawn) were reinserted into multiple logistic regression to yield the models with varying p-value stay and imputation of remaining missing left atrial size values (Table 15). All three methods of variable selection: forward, backward and stepwise, yielded the same variables in the logistic model. The value for missing left atrial sizes were imputed based on a clinical observation that missing

values were not at random. Patients with normal left ventricular function on the angiogram often did not get an echocardiogram and as such those missing values for left atrial size were most likely normal. In models 1 and 3, the left atrial sizes were left blank and models 2 and 4 had the 49 missing values were assumed to be normal. The first model has variables that include age ≥65 years old, mitral valve disease and hypothyroidism. Interesting, by imputing the missing left atrial size values, hypothyroidism was no longer significantly associated and was replaced by left atrial size. The imputations of the missing left atrial sizes were the only sensitivity analyses that changed the variables in the model, the remaining 4 permutations of missing data had the same variables (Table 16). The beta-coefficients and c-statistic in analyses 3-6 were all similar. If all 49 missing left atrial values were assumed normal then, hypothyroidism fell out of the model and left atrial size replaced it. However, if all missing left atrial sizes were assumed to be dilated then hypothyroidism fell out of the model to leave only age and mitral valve disease. The fact that such a small number of missing values would make that much difference in the regression model, lead us to consider the clinical implication of left atrial size as it pertains to the risk of the development of atrial fibrillation.

Table 15
Four Logistic Regression Models Predicting New Onset Postoperative Atrial Fibrillation

Variable		β-coeff	Odds Ratio	95% CI for OR	p-Value	C-statistic (95% CI)	Hosmer & Leme-show p-value	Chi-square/ degrees of freedom
Model 1: 49 missing left atrial sizes , p-entry=0.2, p-stay=0.05						0.678 (0.643-0.714)	0.6795	2.307/4
Age ≥65 years		0.9064	2.475	(1.833,3.342)	<.0001			
Mitral valve disease					<.0001			
	mild vs normal	0.5960	1.815	(1.319,2.496)	0.0002			
	moderate-severe vs	1.1837	3.266	(2.131,5.005)	<.0001			

	normal							
Hypothyroidism		0.4228	1.526	(0.984,2.368)	0.0591			
Model 2: missing left atrial sizes=normal, p-entry=0.2 p-stay=0.05						0.679 (0.643-0.715)	0.3371	5.695/5
Age ≥65 years		0.9418	2.564	(1.903,3.456)	<.0001			
Mitral valve disease					<.0001			
	mild vs normal	0.4916	1.635	(1.174,2.276)	0.0036			
	moderate-severe vs normal	0.9629	2.619	(1.643,4.174)	<.0001			
Left atrial size		0.3516	1.421	(1.033,1.955)	0.0307			
Model 3: missing 49 left atrial sizes , p-entry=0.2 p=stay = 0.15						0.694 (0.658-0.730)	0.6963	4.702/7
Age ≥65 years		0.9328	2.542	(1.862,3.470)	<.0001			
Hypertension		0.3179	1.374	(0.964,1.958)	0.0785			
Mitral valve disease					<.0001			
	mild vs normal	0.5030	1.654	(1.178,2.321)	0.00371			
	moderate-severe vs normal	1.1210	3.068	(1.888,4.985)	<.0001			
Left atrial size		0.2901	1.337	(0.965,1.851)	0.0809			
Hypothyroidism		0.4508	1.570	(0.998,2.468)	0.0509			
Model 4: missing left atrial size values=normal, p-entry=0.2 p=stay =0.15						0.684 (0.648-0.720)	0.3273	6.9305/6
Age ≥65 years		0.9143	2.495	(1.848,3.369)	<.0001			
Hypertension		0.2794	1.322	(0.934,1.872)	0.1150			
Mitral valve disease					<.0001			
	mild vs normal	0.4822	1.620	(1.163,2.256)	0.0043			
	moderate-severe vs normal	1.0302	2.802	(1.742,4.507)	<.0001			
Left atrial size		0.3428	1.409	(1.024,1.939)	0.0354			
Hypothyroidism		0.4003	1.492	(0.958,2.324)	0.0765			

CI=confidence interval OR=odds ratio

Table 16
Sensitivity Analysis for Multivariable Logistic Regression Model Assessing Importance of Missing Data

Variable	β-coefficient	p-value
Original model with missing data, p-entry=0.2 p-stay=0.05		c=0.678(95% CI:0.643-0.714)
Age ≥65 years	0.9563	<.0001
Mitral valve disease		
mild vs normal	0.5769	0.0006
moderate-severe vs normal	1.2286	<.0001
Hypothyroidism	0.4663	0.0425
Sensitivity analysis 1: assumed 49 missing left atrial size = normal		c=0.679(95%CI:0.643-0.715)
Age ≥65 years	0.9676	<0.0001
Mitral valve disease		
mild vs normal	0.4686	0.0061
moderate-severe vs normal	0.9691	<0.0001
Left atrial size	0.3392	0.0389
Sensitivity analysis 2: assumed 49 missing left atrial size=abnormal		c=0.675 (95%CI:0.640-0.711)
Age ≥65 years	0.9658	<0.0001
Mitral valve disease		
mild vs normal	0.5611	0.0007
moderate-severe vs normal	1.1685	<0.0001
Sensitivity analysis 3: assumed 5 missing left ventricular function = normal		c=0.684 (95%CI: 0.648-0.720)
Age ≥65 years	0.9563	<0.001
Mitral valve disease		
mild vs normal	0.5769	0.0006
moderate-severe vs normal	1.2286	<0.0001
Hypothyroidism	0.4663	0.0425
Sensitivity analysis 4: assumed 5 missing left ventricular function =severe		c=0.684 (95%Ci: 0.648-0.720)
Age ≥65 years	0.9563	<0.0001
Mitral valve disease		
mild vs normal	0.5769	0.0006
moderate-severe vs normal	1.2286	<0.0001
Hypothyroidism	0.4663	0.0425
Sensitivity analysis 5: assumed 30 missing right ventricular function = normal		c=0.686 (95%CI: 0.650-0.722)
Age ≥65 years	0.9604	<0.0001
Mitral valve disease		
mild vs normal	0.5997	0.0003
moderate-severe vs normal	1.2269	<0.0001
Hypothyroidism	0.4766	0.0371
Sensitivity analysis 6: assumed 30 missing right ventricular function = severe		c=0.686 (95%CI: 0.650-0.722)
Age ≥65 years	0.9604	<0.0001
Mitral valve disease		
mild vs normal	0.5997	0.0003
moderate-severe vs normal	1.2269	<0.0001
Hypothyroidism	0.4766	0.0371

4.4.3 *Final Logistic Regression Model*

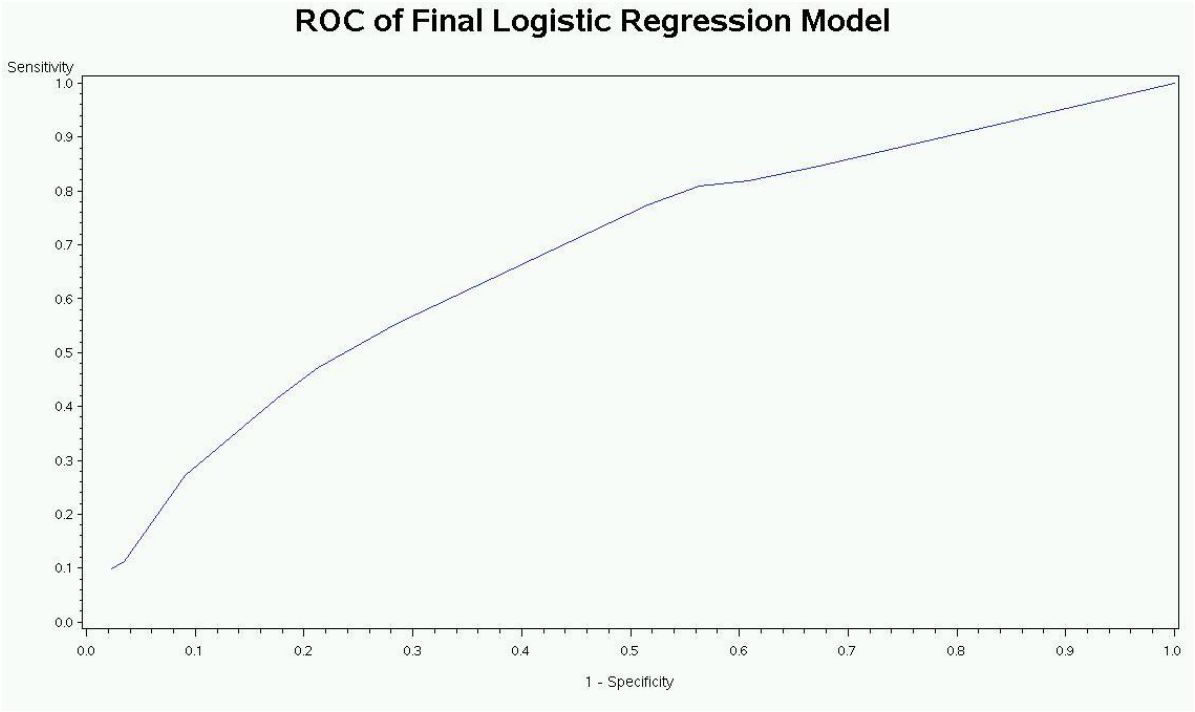
In considering the choice of our final model, heavy emphasis was placed on variables that were clinically intuitive. Age, severity of mitral valve disease and left atrial dilatation all have well documented association with the development of atrial fibrillation (El-Chami et al. 2012, Silva et al. 2010, Rostagno et al. 2010). Hypothyroidism on the other hand did not have a clear pathological link to atrial fibrillation. Also the perioperative anesthesia database documents only patients with hypothyroidism on medication, those who are not on prescription drugs are not represented. When comparing models with different p-stay, the more liberal $p<0.15$ parameter brings in a new variable, 'hypertension', which is also not a useful variable in a prediction rule because it is so prevalent in the study population (73.2%). All things considered, the final model chosen for the prediction rule was model number 2 which includes age ≥65 years of age, mitral valve disease and left atrial size with a p-entry (criteria for variable to be entered into logistic model in stepwise selection) of 0.05 and p-stay of 0.05. The most significant predictor of new onset postoperative atrial fibrillation was moderate to severe mitral valve disease with an odds ratio of 2.6 (95% CI 1.6-4.2).

4.4.4 *Predictive Performance of the Models*

Discrimination of the models was assessed using the c-statistic and calibration, using the Hosmer and Lemeshow goodness-of-fit test. The results of those analyses are presented in Table 12. All four models have similar c-statistics, ranging from 0.679 to 0.687, indicating a fair discrimination. The Hosmer and Lemeshow p-values had a wider range from 0.3933 to 0.8775, all of which are not significant, indicating good model fit for all four models. Figure 2 is the

receiver operating curve for the final logistic regression model with a c-statistic of 0.679 (95% CI: 0.643-0.715).

Figure 2
Receiver Operating Curve for the Final Logistic Regression Model Predicting New Onset Postoperative Atrial Fibrillation c=0.679



4.4.5 New Onset Postoperative Atrial Fibrillation Score

Instead of having clinicians interpret the weight of beta-coefficients, we simplified the prediction model into a scoring system to facilitate its clinical use (Table 20). The probabilities of developing postoperative atrial fibrillation for each level of the score are summarized in Table 15. A patient 65 years of age and older would be given a score of 3 corresponding to a 31.8% chance of developing new onset atrial fibrillation. In contrast a 68 year old who also has severe mitral valve disease and accompanying left atrial dilatation would be assigned the maximum prediction score of 7 and have a 63.8% chance of developing the arrhythmia.

Table 17
New Onset Postoperative Atrial Fibrillation Prediction Score

Variable		β-coefficient	Point
Age ≥ 65 years		0.945	3
Mitral valve disease			
	Mild Moderate-severe	0.4942 0.9704	1 3
Left atrial size		0.3521	1

Table 18
Probabilities of Developing New Onset Postoperative Atrial Fibrillation Associated with Score

Prediction Score	Probability of New Onset POAF	95% CI for the Probability	Sensitivity	Specificity
0	14.7 %	(11.7, 18.0)	1	0
1	19.4%	(16.4, 22.0)	0.845	0.328
2	25.1%	(22.2, 28.2)	0.809	0.437
3	31.8%	(28.8, 34.9)	0.773	0.485
4	39.4%	(35.7, 43.2)	0.544	0.724
5	47.6%	(42.5, 52.6)	0.272	0.910
6	55.8%	(49.3, 62.1)	0.111	0.966
7	63.8%	(56.0, 70.9)	0.098	0.977

POAF= postoperative atrial fibrillation

4.5 Recursive Partitioning

4.5.1 Candidate Decision Trees

As in the case with logistic regression, the variables that underwent recursive partitioning were the twenty two that met the cut-off of $p<0.2$ on the univariate analysis. Thirty seven iterations of prediction rules were explored, but only ten rules fulfilled the 80% sensitivity criteria that had been established a priori (Table 19). For categorical data with more than two categories, all combinations of category collapsing were attempted and only the model with the best sensitivity and specificity are shown.

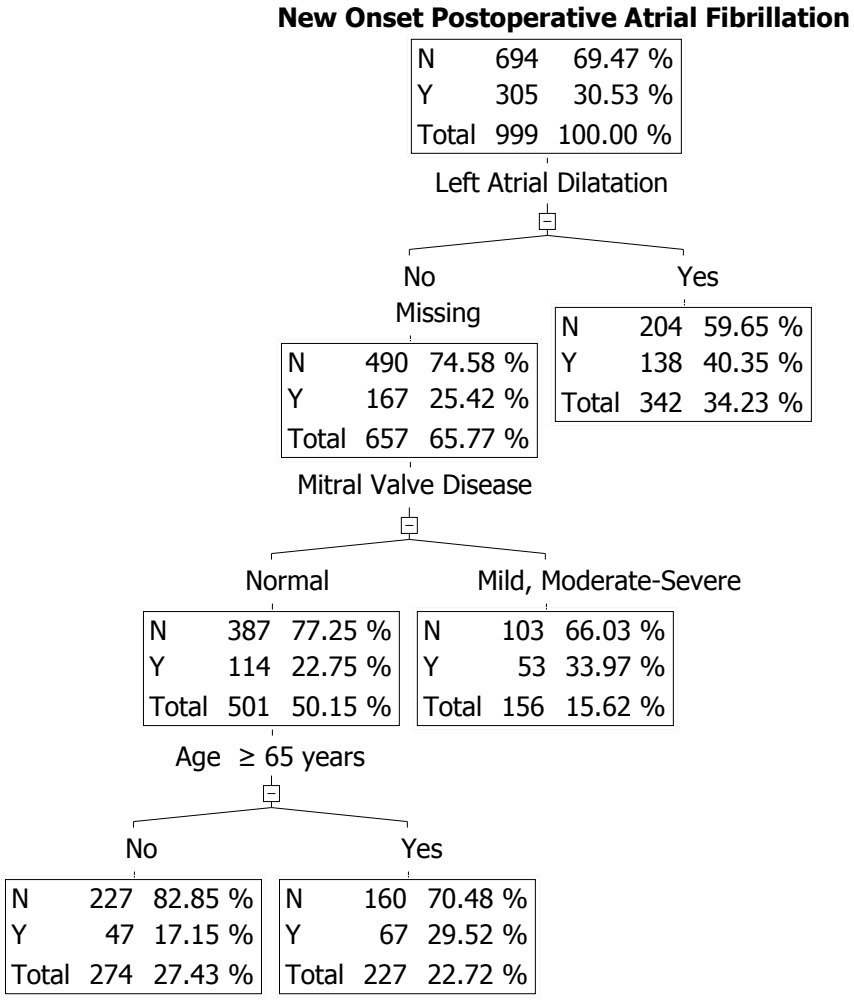
Table 19
Candidate Recursive Partitioning Models with Calculated Sensitivities and Specificities

Model #	Variable 1	Variable 2	Variable 3	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
1	Mitral valve disease (normal vs abnormal)	Age ≥ 65 years	NYHA class heart failure (normal or mild vs moderate-severe)	85.9 (81.4-89.5)	35.2 (31.6-38.9)
2	Chronic obstructive pulmonary disease	Left atrial size	Age ≥ 65 years	85.9 (81.4-89.5)	34.4 (30.9-38.1)
3	Left atrial size	Mitral valve disease (normal vs abnormal)	Age ≥ 65 years	84.6 (79.9-88.4)	39.5 (35.8-43.2)
4	Valve surgery	Age ≥ 65 years		86.2 (81.7-89.8)	33.0 (29.5-36.7)
5	Renal failure	Left atrial size	Age ≥ 65 years	84.6 (79.9-88.4)	33.9 (30.4-37.5)
6	Surgery type (CABG vs combination or valve)	Age ≥ 65 years		86.6 (82.1-90.1)	32.7 (29.2-36.4)
7	NYHA class heart failure (normal or mild vs moderate-severe)	Left atrial size	Age ≥ 65 years	85.9 (81.4-89.5)	33.7 (30.2-37.4)
8	Chronic obstructive pulmonary disease	Age ≥ 65 years	Mitral valve disease (normal vs abnormal)	84.6 (79.9-88.3)	35.9 (32.3-39.6)
9	Surgery type	Hypothyroidism	Age ≥ 65 years	87.2 (82.8-90.6)	31.6 (28.1-35.2)
10	Left ventricular function (missing/normal/ mild vs moderate /severe)	Age ≥ 65 years	Surgery type (CABG/combo vs valve)	87.5 (83.1-90.0)	32.9 (29.4-36.5)

NYHA= New York Heart Association class heart failure; CABG=coronary artery bypass grafting; CI=confidence intervals

4.5.2 Final Prediction Rule Model and Classification Performance

Figure 3
Final Recursive Partitioning Model Predicting New Onset Postoperative Atrial Fibrillation:
Variables: left atrial size, mitral valve disease and age ≥65 years



After eliminating decision trees based on sensitivity criteria, the remaining rules had their specificities compared and the tree with the highest specificity was chosen. Figure 3 is the patient flow diagram for model #3 chosen because it had the minimum requirement of at 80% sensitivity as the lower limit of the 95% confidence interval and the highest specificity, 39.5%.

Coincidently the three variables in the recursive partitioning model are the same ones that are in the final logistic regression model. The sensitivity of the logistic regression model is not as good as the recursive partitioning model. At a level of 25% probability of having the outcome, the sensitivity is 80.9% with a specificity of 56.3%, compared to the recursive model's 84.6% sensitivity and 39.5% specificity.

4.6 Internal Validation

4.6.1 Multivariable Logistic Regression Model

The mean β-coefficients for the 5000 bootstraps of the logistic regression model are summarized in Table 20 along with the standard deviations of the mean and the 95% confidence intervals. Column two of the chart lists the original coefficients from the model and comparison with the bootstrap mean reveals that the values are comparable, supporting the consistency of the model. The c-statistic from the 5000 bootstraps is also similar 0.679 vs 0.680 (95% CI 0.680, 0.681) and is recorded at the bottom of the chart.

Table 20
Mean β-coefficients after Bootstrapping of Final Logistic Regression Model with Standard Deviations.

Variable		β-coefficient from model	5000 Bootstraps			
			Mean β coefficient	SD	Coefficient of variation	95% CI
Age ≥ 65 years		0.942	0.945	0.150	0.159	(0.651,1.239)
Mitral valve disease						
	mild vs normal	0.492	0.494	0.164	0.332	(0.172,0.816)
	mod-severe vs normal	0.963	0.970	0.241	0.248	(0.498,1.443)
Left atrial dilatation		0.352	0.352	0.160	0.454	(0.038,0.665)
			Estimate		95% CI	
C- statistic		0.679	0.680	0.0183	(0.6796, 0.6806)	

SD=standard deviation

4.6.2 Recursive Partitioning Model

The final recursive partitioning model was also bootstrapped 5000 times to give a mean sensitivity estimate of 82.0% (95%CI: 77.6, 86.2) compared to 84.6% (95%CI: 79.9, 88.4). This is acceptable since the re-sampled estimate is within the 95% confidence limit of the original sensitivity model. The specificity from the bootstrapping procedure was 39.2% (95%: 35.5, 42.8) compared to 39.5% (95%CI: 35.8, 43.2) in the model, with no significant difference.

Chapter 5: Discussion

5.1 Overview

To summarize, this study collated prospectively collected data from the Perioperative Database at the University of Ottawa Heart Institute to derive a simple clinical rule for predicting new onset postoperative atrial fibrillation after cardiac surgery. The most relevant predictor variables were determined by specialist consensus and were extracted from the databases and focused chart review. Nine hundred and ninety-nine patients met eligibility criteria, of whom 305 developed the primary outcome. Prediction rule derivation was performed using two different statistical methods: multiple logistic regression and recursive partitioning. The final model from both methods incorporate the same three predictor variables: age, mitral valve disease and left atrial dilatation. The fact that the two methods identified the same risk variables gives more credibility to the proposed clinical prediction rule. Internal validation of both models was performed by bootstrapping and confirmed the reproducibility of the predictions by both models.

5.2 Decisions Pertaining to Model Building Process

5.2.1 Choice of Predictor Variables

The predictor variables chosen for extraction from the databases and chart reviews were compiled from a review of the literature, more importance was given to larger studies. It was uncertain what the incidence of the outcome would be; too many candidate predictor variables would necessitate a larger sample size if the incidence rate turned out to be lower than predicted. A consensus meeting eliminated variables such as brain natriuretic peptide (blood serum marker), ethnic background, diastolic dysfunction (data not available) and

rheumatic heart disease. Of note, some variables, although not very clinically important, were kept on the list because they were easily accessible in the database (hypothyroidism, right coronary artery stenosis, preoperative medications). The plan was for univariate analyses to determine the final list for entry into both modelling strategies.

5.2.2 *Data Extraction and Definitions*

Several decisions were made to optimize data completeness and satisfy clinical implementation. First of all, although it would have been ideal to have exact left atrial size measurements from the echocardiogram reports, this data was missing in one third of the cases. This variable was redefined as a qualitative description of the left atrial size which improved the dataset to only 5% missing values. This step required going back to review every echocardiogram report in the study, ensuring all the data related to these reports were as precise as possible. The remaining few missing data points for left atrial size were then reviewed again, all of these patients were reported to have normal left ventricular systolic function on an angiogram and as a result did not have a preoperative echocardiogram performed. Because left atrial size in this population was not missing at random and it was clinically unlikely that these patients would have an abnormally enlarged left atrium, the 49 missing values were imputed to have normal atrial size. This imputation altered the third variable in the logistic regression model from hypothyroidism to left atrial dilatation. The logistic regression section below will discuss this point. All categorical variables with more than two levels were collapsed into fewer categories to simplify the number of levels that a clinician would have to recall in the final rule. This included the extensive data on the grades of ventricular function and valvular disease. Clinical judgement was exercised to convert these values to mild, moderate and severe disease. It was the hope of the authors that the different

levels (as opposed to yes/no) would improve the classification performance of the recursive partitioning model.

5.2.3 *Univariate Analyses*

Fourteen predictor variables were found to have statistically significant associations with the primary outcome: age, renal failure, chronic obstructive pulmonary disease, hypothyroidism, New York Heart Association (NYHA) heart failure class, right ventricular function, left atrial dilatation, valvular disease, mitral valve disease, preoperative digoxin use, surgery type, valve surgery (more specifically mitral valve surgery) and Cardiac Anesthesia Risk Evaluation score (CARE Score). The CARE score is validated risk index comprising of four variables designed to facilitate quick preoperative prediction of morbidity and mortality after cardiac surgery (Dupuis et al 2001). All these variables were decided to be of clinical importance except for hypothyroidism for which its pathologic link to atrial fibrillation was unclear and preoperative digoxin use which had a very low (0.8%) prevalence in the study population. They were kept in the candidacy list however because the high incidence of the outcome measure did not preclude the number of variables used in the modelling step. Another nine variables were inserted into modelling because they met the cut-off p-value of 0.2.

5.2.4 *Multiple Logistic Regression*

We considered four different logistic regression models before finalizing the model. The four models differed in the selection criteria for staying in the logistic model (p=0.05 or p=0.15) and how the missing left atrial dilatation variable was imputed (nothing or normal). Preliminary modelling included the CARE Score in the model, this variable however was removed because having a score as the component of another score would defeat the simplicity of the rule. With

the remaining three variables (age, mitral valve disease and hypothyroidism), we found that increasing the p-value for staying in the model 3 brought in hypertension (p=0.08) and left atrial dilatation (p=0.08). On the other hand, when the missing left atrial values were imputed to be normal, hypothyroid falls out of the model. This is a situation where clinical judgement is important. Left atrial size has a more plausible pathophysiological mechanism predicting atrial fibrillation than hypothyroidism (Manning, Gelfand 2006). The definition of hypothyroidism in the database captures those on supplementation only, resulting in two types of misclassification: 1) omitting those patients with subclinical hypothyroidism not on medications; and 2) including those patients having undergone thyroid ablation for hyperthyroidism, now on supplementation. Although there have been reports of hypothyroidism being associated with atrial fibrillation, it is actually hyperthyroidism that is more often associated with atrial fibrillation in the non-surgical population (Frost, Vestergaard & Mosekilde 2004). When comparing the logistic regression model to recursive partitioning, the sensitivity for the recursive model is better, even though they consist of the same three variables. This is the results of the differences in the two statistical methods use for derivation. The final logistic model was converted into an atrial fibrillation prediction score based on the beta coefficients in the model to facilitate use in a busy clinical practice.

5.2.5 Recursive Partitioning

Multiple models were explored using recursive partitioning. Splitting the decision tree at different grades of severity for the multilevel variables (left ventricular function, NYHA class, valve disease) did not yield a suitable discrimination of the groups. This was most likely because the sample size was not large enough to allow for differentiation between the different severities of disease. Model selective with recursive partitioning was performed solely based on

choosing the prediction tree with the best specificity with the minimum sensitivity threshold. It is markedly unusual for both logistic regression and recursive partitioning to arrive on the same three predictor variables, as it did in this study.

5.3 Comparisons with Reported Literature

5.3.1 Epidemiology of New Onset Postoperative Atrial Fibrillation

The incidence of new onset postoperative atrial fibrillation (30.5%) was similar to that previously reported (25.6% (Mariscalco, Engstrom 2008), 29.7% (Rostagno et al. 2010), 32% (Thoren et al. 2012)). In Mariscalco's study of 1832 patients, 26 patients died, a significantly higher proportion of which were patients with atrial fibrillation, 19/26 (3.3% of those with atrial fibrillation) compared with 7 (0.5%), $p<0.001$ (Mariscalco et al. 2008). This is consistent with our finding in this study where 2.6% of the patients with new onset atrial fibrillation did not survive until hospital discharge. Also in keeping with previous reports was the increased perioperative morbidity in those patients with new onset atrial fibrillation. These patients had a higher incidence of pulmonary edema, acute renal failure, mesenteric ischemia, gastrointestinal bleeds, readmission to the intensive care unit and longer hospital lengths of stay. The above mentioned Italian study of 1832 patients reported an increased incidence of stroke, intra-aortic balloon pump use, infections and respiratory failure. A Swedish study of 7115 patients (Thoren et al) reported an increased hospital length of stay and a higher incidence of stroke, heart failure, re-operation, hemodynamic instability, diminished renal function, respiratory complications, heart failure, increased intensive care stay but not in-hospital mortality. We were unable to find an increased risk of stroke in our study, possibly because our sample size was smaller than the two above mentioned studies.

5.3.2 *Comparison with Other Risk Scores and Indices*

One major objective of this study is to develop a preoperative tool to identify patients at risk of new onset postoperative atrial fibrillation (POAF). The reason for this is that most existing therapies with proven efficacy to prevent POAF must be started before or during surgery. With the exception of one risk index, all existing atrial fibrillation prediction models have included intraoperative or postoperative parameters, which make them useless to target patients who are most likely to benefit from preventive therapies of atrial fibrillation. Bearing this in mind, select aspects of the models will be discussed below for comparison with our study.

Mahoney *et al* in their analysis of the cost-effectiveness of targeted intravenous amiodarone used multivariable logistic regression to find predictors of atrial fibrillation specific to the type of surgery being performed. As in our case, their analysis was performed on prospectively collected data from an institutional database (Mahoney et al. 2002). The sample size was 10 550 patients undergoing surgery in one surgical center from January 1994 to June 1999. The study derived separate models for coronary bypass, valve and combination procedures. For patients undergoing coronary bypass: increasing age, longer cardiopulmonary bypass time, male sex and previous myocardial infarctions were predictors for postoperative atrial fibrillation. The c-statistic associated with this model was 0.676 (similar to our model's value of 0.679) and 0.675 after 150 bootstraps. For valve surgeries (c-statistic 0.665), they found that chronic obstructive pulmonary disease was predictive of atrial fibrillation while current smoking was protective. Neither of these variables were significant in our study. For combined procedures, the model had only two predictive variables: increasing age and renal failure (c-statistic 0.645). The authors mentioned that they had to perform multiple imputations for missing data and had to fit the model using cubic spline functions(demonstrating the difficulty in

fitting the data to one simple function). This may explain why the goodness of fit for procedures involving valves was not as high. Atrial fibrillation was associated with a 3.3-6.4 day increase in length of stay depending on the procedure the patient underwent. The report also described how much money different thresholds for initiating preventative therapy (intravenous amiodarone) would save, assuming 26% effectiveness of amiodarone and cost of $973 per 1 g/day for 2 days of amiodarone. For a predicted probability of developing atrial fibrillation of 25% they reported that the average cost/event averted would be $7, 891 for a hospital stay. This threshold of 25% probability would be equivalent to a patient having an atrial fibrillation prediction score of 2/7 in our derived prediction rule. Although one could argue that the derivation of separate risk models for each type of surgery is more patient specific, one could also argue that this limits the generalizability of this work because the busy clinician will not remember which factors are important in which situation.

Mathew *et al* developed a multicenter Risk Index for postoperative atrial fibrillation (POAF) using 4657 patients undergoing coronary artery bypass grafting (Mathew et al 2004). The incidence of POAF was 32.3%. However, that was not only new onset atrial fibrillation since preoperative atrial fibrillation is one of the components of their risk index. The points system consists of 10 factors and is complex. The score is weighted heavily by age (6 points for every decade of life beyond 30) which is added to points from preoperative history (chronic obstructive pulmonary disease, atrial fibrillation), drug withdrawal (beta-blockers and ace inhibitors) and then points for protective postoperative treatment medications are subtracted. The total possible score is 60, for which a medium risk is defined as a score of 14-31 corresponding to a 17-52% risk of developing postoperative atrial fibrillation. This wide range is equivalent to a score of 1-6 on the prediction score derived in our study. The model for this risk

index by Mathew *et al* had an area under the receiver operating curve of 0.77, which is better than the 0.68 in our study model. Although one could argue that these two studies are not comparable at all, due to the large difference in predictor variable composition. The inclusion of postoperative factors and complexity (10 variables) of this score calculation (total 60) are the most likely reasons why this index is not widely used to predict postoperative atrial fibrillation. An interesting sub-analysis in this data found that patients who had recurrent episodes of atrial fibrillation were at higher risk of longer length of hospital stay, increased infection rates, renal impairment and neurological complications compared to those who had one single episode.

Another prediction rule was derived using clinical variables and standardized measurements on the electrocardiogram in 1851 patients undergoing coronary artery bypass grafting. The final model included age, history of atrial fibrillation, P-wave duration >110 milliseconds on the electrocardiogram and postoperative low cardiac output (Amar et al. 2004). The model discrimination in this case was depicted by an area under the receiver operating curve (ROC) of 0.69. The coefficients from the logistic regression model were converted to a point score out of 110 for predicting the probability of atrial fibrillation. Cut-offs chosen for their point score corresponded to: 14% (mild), 36% (moderate) and 59% (high) chance of developing postoperative atrial fibrillation. This prediction rule included patients with preoperative atrial fibrillation as well as postoperative weak heart function and would not be directly comparable to our study population. Also a point score out of 110 is difficult to remember at the bedside or in clinic. This same group derived a prediction rule for postoperative atrial fibrillation after noncardiac thoracic surgery (Passman et al. 2005). It is interesting that the final model derived from a cohort of 856 cancer patients undergoing thoracic surgery included: male sex, advanced age and preoperative heart rate >72 beats per minute. Age seems to be a predictor variable that

is consistently associated with atrial fibrillation regardless of the clinical scenario with and without surgery (Amar et al. 2002).

A few other reports have been recently published on prediction of postoperative atrial fibrillation. One of them is a Swedish study of 7115 patients who had coronary artery bypass grafting over a period of 13 years (Thoren et al 2012). The population in that study included all patients in sinus rhythm at the time of surgery, even those with a previous history of atrial fibrillation. That is slightly different from our study which excluded all patients with a history of atrial fibrillation, even if their heart rate was normal at the time of surgery. Using logistic regression, the authors identified 10 predictors of postoperative atrial fibrillation: advancing age, male sex, current smoking, previous myocardial infarction, renal insufficiency, New York Heart Association heart failure class IIIA increased the risk of atrial fibrillation and hyperlipidemia was protective. However, the protective effect of hyperlipidemia was minor with an odds ratio of 0.9 (95%CI 0.8-1.0). Discrimination of the model was only fair with an area under the ROC curve of 0.62 (95% CI 0.61-0.64). The authors concluded that their study confirms that prediction of postoperative atrial fibrillation is challenging. The model did not predict postoperative atrial fibrillation was well as this study and no validation step was performed; a necessary step before implementation of the model.

Another recently published report by El-Chami et al derived a risk index for new onset postoperative atrial fibrillation from 18 517 bypass patients registered in the Society of Thoracic Surgery national database (El-Chami et al. 2012). The risk index was derived using logistic regression and validated with a subsequent cohort of 1378 patients. The outcome measure in this study was defined as documented postoperative atrial fibrillation or atrial flutter (a regular

atrial arrhythmia) necessitating treatment (including all heart slowing medications, blood thinners and cardioversion). As a result, the outcome measure is not strictly new onset atrial fibrillation but a composite of supraventricular tachycardias. The definition of 'treatment' differed from our study where treatment is defined as amiodarone administration or electrical cardioversion. The use of heart slowing medications and blood thinners is ambiguous because there are other common indications (i.e. coronary artery disease, low ejection fraction, prosthetics valves etc.) to prescribe those medications. The five point atrial fibrillation index was based on four variables (with different cut-off levels for men and women): age (67.5 vs 61.3 years), height (172.3 vs 171.2 cm), weight (86.6 vs 85.7 kg) and the presence of peripheral vascular disease. The model had an area under the ROC of 0.68. It is important to mention that although the variables height and weight are statistically significant, they are not necessarily clinically significant. From a pathophysiological point of view, it is difficult to associate a 1 cm difference in height or a 900g difference in weight with an increased risk of atrial fibrillation. Consequently, the study raises concern regarding the methodology used to identify risk predictors in medicine. This is an example where a large enough sample size (>18 000) would have sufficient power to find a statistical difference in any continuous variable. The authors mentioned that body mass index (contains height and weight indexed to body surface area) was not significantly different, hence atrial fibrillation might not be associated with obesity. Body mass index was found to be insignificant in our study as well, although it has been reported to be important elsewhere (Wang et al. 2004). The investigators reported a 16cm increase in height would increase the probability of developing atrial fibrillation by 50% from baseline. Height and weight might be a surrogate marker for larger atrial size (a variable that was not collected in their database). Although we did not include *a priori* height and weight in the list of

predictors for inclusion into our prediction rule, we have left atrial size instead which has established clinical correlation with atrial fibrillation. Preliminary application of this risk index to our dataset demonstrated poor discrimination of the model for both men (c-statistic of 0.621) and women (c-statistic of 0.591). This result highlights the need for a validation step in prediction rule methodology.

In summary, it is clear that the discrimination of all existing predictive models for postoperative atrial fibrillation are only fair; this study being no exception. This is most likely due to the following reasons: 1) multifactorial etiology of postoperative atrial fibrillation; 2) some causes or risk factors of postoperative atrial fibrillation are still unknown and 3) the heterogeneity of the cardiac surgical population under study (different pathologies of varying severity, different preoperative medications, different preoperative co-morbidities).

5.4 Strengths and Limitations of study

This clinical prediction rule derivation uses data from a retrospective chart review directed by prospectively collected institutional databases. This type of study has inherent challenges due to its retrospective nature and the inability to control what data is collected. In the following section we shall discuss the strong points and weaknesses of this study.

5.4.1 Strengths of Study

The major strength of this study is that it used two different methods to develop a preoperative clinical predictive rule for postoperative atrial fibrillation. Instead of simply using traditional logistic regression to derive a clinical prediction rule, this study implemented two different statistical methods: multiple logistic regression and recursive partitioning. These two

methods do not often arrive upon the same model, but it did in our dataset. The fact that the two methods identified the same risk variables in our clinical prediction rule give robustness to the proposed predictive model.

Another strength is the large size of the study and the high incidence of the outcome measure, allowing for assessment of more than 25 predictor variables. Data from the most recent calendar year was used in order to minimize any unmeasured difference in clinical care from that of present day. To diminish misclassification of the primary outcome, every patient meeting demographic and procedural inclusion criteria was reviewed. The most common reason for elimination from the study after chart review was the presence of preoperative atrial fibrillation. Supplementation of the database extraction with chart review allowed for thorough targeted collection of all the predictor variables that were not included in the database. Each chart reviewer was audited by a second reviewer, including the principal investigator, revealing a concordance of greater than 92%. There was complete in hospital follow-up of these patients, with a high lost-to-follow-up after hospital discharge.

The method used for internal validation of the proposed model was another strength of our study. It was performed by bootstrapping both models 5000 times yielding very consistent reproducibility of the risk estimates of the prediction rule. The results obtained through that validation process confirm the robustness of the proposed model and warrant progression onto the next step: prospective validation. A simple postoperative atrial fibrillation risk score was derived consisting of only three variables (age ≥65 years of age, mitral valve disease and left atrial dilatation) for a total possible score of 7, allowing for prediction of moderate to high risk patients with a score of greater than 3.

5.4.2 Study Limitations

As previously highlighted, the cause of postoperative atrial fibrillation is multifactorial and no definite mechanism has been delineated. Multiple reports have demonstrated the association between the development of postoperative atrial fibrillation and long term mortality. It is an assumption that atrial fibrillation has a causal relationship with long term mortality as opposed to it being a marker for another process in these higher risk patients. The treatment of atrial fibrillation also entails complications that could increase mortality such as over-anticoagulation leading to bleeding or too much beta blockade leading to heart block and syncope. Until the link between postoperative atrial fibrillation and morbidity or mortality is better delineated, diminishing the incidence of postoperative atrial fibrillation cannot be undertaken with the certainty that it will result in better outcome after cardiac surgery.

The most important shortcoming of this study is arguably the retrospective nature of the study and the inability to directly confirm the primary outcome. Database maintenance, from data collection and verification to database entry are managed by dedicated trained personnel with healthcare experience. New onset atrial fibrillation is tagged if the patient had no history of atrial fibrillation and developed an irregularly irregular heart rhythm observed on electrocardiogram (by telemetry or 12-lead ECG) or required treatment to relieve symptoms. These events were not witnessed by the research assistants themselves but were abstracted from daily chart review. It is possible that events not appropriately recorded would have been missed. Upon discharge from the intensive care unit to the ward, patients were not routinely monitored on telemetry (continuous electrocardiogram monitoring). The onus is on symptomatic patients to bring it to the attention of a health care provider. Ideally the patients should be on 24 hour recorded electrocardiogram monitoring throughout the hospital stay.

However this would be impractical to perform especially in patients with prolonged length of stay. The definition of atrial fibrillation in reported studies have ranged from 30 seconds to 30 minutes of asymptomatic atrial fibrillation or unstable onset requiring treatment. This inconsistency explains the various reported incidences of postoperative atrial fibrillation. Due to the recognized weakness of a retrospective chart review, a prospective internal validation study will be performed to test the new clinical prediction rule before moving forward onto a multicenter validation study.

Two of the three predictor variables in the prediction rule are obtained from the echocardiogram of the patient, either preoperative transthoracic or intraoperative transesophageal before cardiopulmonary bypass. Although there are standards for the acquisition of echocardiograms as suggested by the American Society of Echocardiography and recommendations for the components of a report, the report is not standardized (Gardin et al. 2002, Shanewise et al. 1999). This is the reason why the left atrial size variable had to be changed from a continuous measurement to a categorical descriptor. All the missing data points (left and right ventricular systolic function and left atria size) were due to incomplete or missing echocardiograms. Improvements with prospective validation should include ensuring that all enrolled patients have a preoperative echocardiogram to enable risk assessment. Ideally the echocardiograms should also be performed at one center, although having tests performed at different sites are a recognized real world reality.

Even though left atrial dimension is a predictor of postoperative atrial fibrillation in our model, more recent studies shown that left atrial volume indexed to body surface area may be a more robust predictor of atrial fibrillation, stroke risk and diastolic function. An indexed left

atrial size <28mL/m^2 is considered normal (Manning, Gelfand 2006, Nardi et al. 2012). Osranek et at the Mayo Clinic, used left atrial volume instead of left atrial size and in a small sample size of 205 patients and found only age and left atrial volume >32ml/m^2 was predictive of postoperative atrial fibrillation. Increased left atrial volume is an indicator of chronic volume or pressure overload that would predispose the patient to atrial fibrillation (Osranek et al. 2006). Conceptually, measuring the volume would be more accurate than measuring left atrial size dimension, on a 2D echocardiogram. They obtained left atrial volume by using a biplanar method indexed to body surface area, a practice that is only now starting to become included in the practice at the University of Ottawa Heart Institute. Because this is an emerging technique, inclusion of this variable in the prediction rule may limit its generalizability as many centers will not have this parameter in their echocardiogram reports.

Due to the large number of clinical predictors (22) incorporated into the multiple logistic regression model, no systematic testing for interactions was performed as this would involve assessing 231 possible combinations. Such multiple testing would certainly lead to positive interactions that would be difficult to decipher, especially with the unclear pathophysiology of atrial fibrillation. With the final model, there were only three variables, one of which is age which would interact with both the other terms. Also mitral valve disease can lead to left atrial dilatation in chronic cases.

6.0 Conclusions and Future Directions

6.1 Conclusions

This project has accomplished what it set out to achieve. We were able to describe the epidemiology of new onset postoperative atrial fibrillation. For those patients who underwent coronary artery bypass grafting and/or valve surgery at our institution in 2010, the incidence of new onset POAF was 30.5%, consistent with reported values. The course in hospital for those who developed new onset postoperative atrial fibrillation was more complicated with an increased number of cardiovascular complications (heart block, cardiac arrest, pulmonary edema), mesenteric ischemia, gastrointestinal bleeding, liver failure and renal failure. These complications lead to an increase readmission rate to the intensive care unit, tracheostomy and higher in-hospital mortality. Only 11% of patients remained in atrial fibrillation by the time they were discharged from hospital. However, one third of patients with new onset postoperative atrial fibrillation were prescribed an antiarrhythmic medication and anticoagulants. By the time of the first post-discharge visit, another 50% of patients were back in sinus rhythm. At which point their atrial fibrillation medications were discontinued. Follow-up after hospital discharge was limited to encounters with The Ottawa Hospital and it was alarming to find that all six cases of mortality were related to atrial fibrillation management, either inadequate therapy or over anticoagulation.

Two models for predicting new onset postoperative atrial fibrillation have been derived using different statistical methods. The final logistic regression model included the predictor variables: age ≥ 65 years, mitral valve disease and left atrial dilatation. The model was then converted into an atrial fibrillation risk score and presented with the associated probability of

developing new onset postoperative atrial fibrillation. This score would facilitate decision making for clinicians as they decide on the threshold of risk at which to initiate preventative therapy on patients. The final recursive partitioning model included the same three predictor variables with a sensitivity of 85% and a specificity of 40%. We performed internal validation by means of bootstrapping to show that our estimates for both models are consistent.

In deciding which model would be more useful in clinical practice, one can weigh the pros and cons of either model. The recursive partitioning model has a higher sensitivity, but must be used as a complete rule. Patients need not have all three variables to be considered at high risk according to the score. A score of 4 implies a 40% probability of developing POAF with a corresponding 54% sensitivity and 72% specificity. One could argue that with the low risk of severe complications associated with preventative therapy, the clinician should prefer a more specific rule. We recommend that the atrial fibrillation score be used to direct atrial fibrillation prophylaxis and a score of 4 is a reasonable threshold to initiate therapy.

6.2 *Future Directions*

6.2.1 *Prospective Validation of Prediction Score*

Having derived a clinical prediction score to forecast the expected incidence of new onset postoperative atrial fibrillation, the next step in prediction score methodology would be to perform a prospective validation of the score. This clinical tool uses data from one cardiac surgery center and should be tested at different surgical sites. However, because this score was based on retrospective chart review with some methodological drawbacks, we plan to perform an internal prospective validation study before embarking on a multicenter validation. In designing the prospective validation for this study, there are several factors that would improve

the quality of our study. Inclusion criteria will be unchanged and all enrolled patients should have a preoperative echocardiogram. Preferably echocardiograms should be performed at the Ottawa Heart Institute. As a matter of interest, left atrial volume indexed to body surface area could be assess concomitantly and compared to left atrial dimension. Twenty-four hour postoperative electrocardiogram monitoring for the entire length of hospital stay will not be possible at our institution due to the limited number of monitoring equipment. In order to maintain consistency with the derivation cohort, the definition of postoperative atrial fibrillation will remain unchanged: an irregularly irregular supraventricular rhythm requiring treatment. Patients will be on telemetry during their stay in the intensive care unit and clinical symptoms or detection on daily electrocardiogram will be used as an outcome end-point for the remainder of the hospital stay (unless the patient's medical management requires telemetry on the ward). A research assistant will follow patients daily until the date of discharge, interview patients at their first postoperative visit and call patients lost to follow-up one month after last contact. The same twenty eight clinical predictors in addition to the indexed left atrial volume (if available) will be collected as well as all important complications and clinical outcomes after surgery. The prospective study will allow for observation of the clinical course and treatment of atrial fibrillation after discharge from hospital, without having to rely on incomplete charts as we encountered in this study. This study will also allow for assessment of ease of use of the score as well as the appropriateness of its implementation.

After the internal validation study is performed, adjustments to the model may be required. The final validated model will then undergo prospective external validation in multiple cardiac surgical centers. The aim would be to assess ease of use, clinician acceptance and the predictive value of the rule outside of its derivation site.

6.2.2 *Preventative Intervention*

Looking forward, after validation of this prediction rule, an evidence based clinical algorithm needs to be developed for the prevention of postoperative atrial fibrillation. A multi-disciplinary approach will be employed involving researchers in pharmacy, cardiac surgery, anesthesia, critical care and nursing to develop this clinical bundle for postoperative atrial fibrillation. The method employed should be flexible and amenable to the unpredictable timing of cardiac surgery. The combined administration of intravenous amiodarone on call to the operating room and conversion to oral amiodarone postoperatively may provide this flexibility. Such an algorithm for prevention of postoperative atrial fibrillation will enable us to determine the impact of our prediction rule both with regards to important clinical outcomes and cost savings. Barriers to the use of the atrial fibrillation prediction score lies in the complexity of the prevention protocol. The cost of the drugs and use of workforce will have to be more economical than the management of complications and increased length of hospital stay associated with patients who have postoperative atrial fibrillation. Implementation of the clinical care bundle with the prediction score would then allow for the assessment of the impact of the prediction score. Hopefully to decrease the burden of postoperative atrial fibrillation and diminish the number of negative clinical outcomes.

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Appendices

Appendix A: Perioperative Cardiac Anesthesia Database Form

UNIVERSITY OF OTTAWA HEART INSTITUTE PERIOPERATIVE DATABASE UNIT Database No. _____ (2011/05/05)

SURGERY: [__]CABG +CPB [__]OPCAB [__]MIDCAB [__]SVST [__]MVST
[__]AVR [__]Repair AV [__]MVR [__]Repair MV [__]Transplant
[__]Homograft AVR [__]TVR [__]Repair TV [__]VAD
[__]Root enlargement + AVR [__]PVR [__]LV aneurysm repair
[__]Bentall [__]VT/VF ablation [__]PTE
[__]Ross [__]AF ablation [__]Other:_____
[__]Transfemoral TAVI [__]ASD/PFO Closure _____
[__]Transapical TAVI [__]Pericardiectomy _____
[__]Valve sparing aortic root replacement _____
[__]Thoracic aorta

SURGEON: [__] Boodhwani [__]Goldstein [__] Hendry [__] Lam
[__] Maharajh [__] Masters [__]Mesana [__] Rubens
[__] Ruel [__] Other:_____

ANESTHETIST: [__] Bourke [__] Cattran [__] Dickie [__] Dupuis
[__] Hudson [__] Hynes [__] Lambert [__] J. Macdonald [__] B. McDonald
[__] Nicholson [__] Robblee [__] Sohmer [__] Tran [__] Wilkes
[__] Resident/Fellow:_____

Date of Surgery: YY_____/MM____/DD____ Sex [__] M [__]F Height_____cm Weight_____kg BMI_____

CARDIAC HISTORY

Angina - Canadian Cardiovascular Society (CCS) Classification
[__] Class 0 (No Angina) [__] Class I [__] Class II [__] Class III
[__] Class IV-A: Angina at rest - Can be managed as outpatient.
[__] Class IV-B: Angina at rest - Requires hospital admission, but no i.v. NTG
[__] Class IV-C: Angina at rest - Requires hospital admission **with i.v. NTG**
[__] Class IV-D: Any coronary syndrome associated with shock

Recent MI (< 6 weeks ago) [__]No [__]Yes
If yes: [__]Q-wave[__]Non-STEMI or non-Q
Remote MI (≥ 6 weeks ago) [__]No [__]Yes
If yes: [__]6 weeks - 6 mo. [__]> 6 mo.
Previous PTCA/Stent [__]No [__]Yes
If yes: [__]< 24 h [__]≤ 6 mo. [__]> 6 mo.

Current CHF Status:
[__] No CHF
[__] NYHA I - No symptoms with ordinary physical activity.
[__] NYHA II - Physical activity slightly limited
[__] NYHA III - Physical activity markedly limited: comfortable at rest
[__] NYHA IV - Inability to carry on any activity: symptoms at rest

Shock (CI < 1.8 and/or SBP <90) [__]No [__]Yes
Currently in Pulmonary Edema [__]No [__]Yes
Right Heart Failure [__]No [__]Yes
Permanent Pacemaker [__]No [__]Yes
Referred by Other ♥ Surgical Centre [__]No [__]Yes
Previous Cardiac Arrest (VF/VT) [__]No [__]Yes
IABP before coming to OR [__]No [__]Yes
Ventricular Assist Device in Place [__]No [__]Yes
If yes: [__] Left [__] Right [__] Total Artificial Heart
If yes: [__] Para-corporeal [__] Intra-corporeal

Cardiac Reoperation (Redo) [__]No [__]Yes
Within same admission [__]No [__]Yes
No. Previous Cardiac Sx (any type) [__] 1 [__] 2 [__] 3 [__] 4 [__] ≥5
Specify No. Previous:

CABG Sx	[__]1	[__]2	[__]3	[__]4	[__]≥5
Single Valve Sx	[__]1	[__]2	[__]3	[__]4	[__]≥5
CABG+Valve Sx	[__]1	[__]2	[__]3	[__]4	[__]≥5
Multi-Valve Sx	[__]1	[__]2	[__]3	[__]4	[__]≥5
Bentall	[__]1	[__]2	[__]3	[__]4	[__]≥5
Transplant	[__]1	[__]2	[__]3	[__]4	[__]≥5
Assist Device/TAH	[__]1	[__]2	[__]3	[__]4	[__]≥5
LV Aneurysmectomy	[__]1	[__]2	[__]3	[__]4	[__]≥5
LV Remodeling	[__]1	[__]2	[__]3	[__]4	[__]≥5
Arrhythmia Sx	[__]1	[__]2	[__]3	[__]4	[__]≥5

[__]Other _____

Aortic Reoperation (Not Involving Heart) [__]No [__]Yes
Within same admission [__]No [__]Yes
No. Previous Aortic Surgery [__] 1 [__] 2 [__] 3 [__] 4 [__] ≥5
Specify No. Previous:

Ascending	[__]1	[__]2	[__]3	[__]4	[__]≥5
Arch	[__]1	[__]2	[__]3	[__]4	[__]≥5
Descending	[__]1	[__]2	[__]3	[__]4	[__]≥5
Abdominal-suprarenal	[__]1	[__]2	[__]3	[__]4	[__]≥5

Endocarditis (currently on antibiotics) [__]No [__]Yes
Infectious Agent_____ Rx started on_____

ASSOCIATED DISEASES

Carotid Disease (documented) [__]No [__]Yes
Subclavian Stenosis (documented) [__]No [__]Yes
Peripheral Vascular Disease (documented) [__]No [__]Yes
Prior Vascular/Carotid Surgery or Angioplasty [__]No [__]Yes
Diabetes Mellitus [__]No [__]Yes
If yes: [__]Untreated or on diet [__]On oral Meds [__]On insulin
Hypertension [__]No [__]Controlled [__]Uncontrolled (>160/105)

OPERATIVE DIAGNOSIS (there may be more than one diagnosis)

1. Coronary Disease [__]No [__]Yes
2. Valvular Disease [__]No [__]Yes
Aortic Valve [__]Native [__]Prosthetic
[__] Stenosis Area_____cm^2 Peak Gradient_____mmHg
[__] Insufficiency Severity Grade 1+ 2+ 3+ 4+
Mitral Valve [__]Native [__]Prosthetic
[__] Stenosis [__]Insufficiency 1+ 2+ 3+ 4+
Pulmonic Valve [__]Native [__]Prosthetic
[__] Stenosis [__]Insufficiency 1+ 2+ 3+ 4+
Tricuspid Valve [__]Native [__]Prosthetic
[__] Stenosis [__]Insufficiency 1+ 2+ 3+ 4+

3. Aortic Disease
Thoracic Aneurysm [__]Asc [__]Arch [__]Desc [__]Thor-Abd
Aortic Dissection [__]Type A-involving the ascending aorta
[__]Type B-not involving the ascending aorta

4. Pericardial Disease [__]Effusion [__]Constrictive
If Effusion → [__]Infectious [__]Tumor [__]Other

5. Tumor [__]RA [__]LA [__] RV [__]LV [__] Renal [__]Pericardium
[__]Other_____

6. Congenital Disease
[__]ASD [__] PFO [__]VSD [__]PDA [__]Tetralogy [__]Vascular Ring
[__]Aortic Stenosis [__]Pulmonic Stenosis [__]Coarctation
[__]Endocardial Cushion [__]Transposition [__]Single ventricle
[__]Other:_____

7. Cardiomyopathy [__]Congenital [__]Ischemic [__]Valvular [__]Viral
[__]Idiopathic [__]EtOH [__]Other:_____

OTHER DATA ON IMMEDIATE OPERATIVE DIAGNOSIS

[__] LV Aneurysm [__]Graft Revision(same admission)
[__]Acute MI (<24 hr) [__] Ventricular rupture
[__]Complication from Cath [__]Arrhythmia history (<24 hr)
[__]Cardiac Arrest (<24 hr) [__]Acquired VSD
[__]Tamponade [__]Ongoing CPR
[__]Chronic Pulmonary Emboli [__]Other_____

OPERATIVE PRIORITY

[__] Elective
[__] Urgent (diagnostic & OR on same admission)
[__] Emergency - **Specify if**:
[__] Immediate (= as soon as OR is available) or [__]Surgery within 24h

ANGIOGRAM

Date of Cath YY____/MM____/DD

Native Coronaries

≥50% Stenosis in territory of [__] LM [__] LAD [__] Ccx [__] RCA

Comments _____

Grafted Vessels

≥50% Graft Stenosis in territory of [__] LAD [__] Ccx [__] RCA

PA Pressure:

1) Preoperative: ___/___ [__] Unknown

[__] By PA catheter [__]By Echocardiography

2) First Intraoperative Reading: ___/___ [__] Unknown

PREOPERATIVE VENTRICULAR FUNCTION

Note - Use Cath Lab classification only if no other measure is unavailable.

Class Ventricle [__] 1 (EF ≥ 50%) [__] 2 (EF 35-49%)
[__] 3 (EF 20-34%) [__] 4 (EF < 20%) [__] Unknown

by: [__] Planimetry/Cath [__]Echo [__] Nuclear Imaging [__] CT Angio
[__] Intraop. TEE (to be used only if no preop LV function is unknown)

Preoperative EF:_____% [__] Unknown

ECG

Atrial Fibrillation [__] No [__] Yes [__] Intermittent

LABORATORY

Hgb_____g/L Hct 0._____ Plat_____ INR_____ Creat_____µmol/L

Other_____

CENTRAL NERVOUS SYSTEM

History of CVA/TIA Unrelated to Carotid Dis.	[__] No	[__] Yes
History of CVA/TIA Related to Carotid Dis.	[__] No	[__] Yes
Post-CVA Residual Neurological Deficit	[__] No	[__] Yes
Seizure Disorder	[__] No	[__] Yes
Parkinson's Disease	[__] No	[__] Yes
Other Debilitating Neurological Disease	[__] No	[__] Yes

Specify:_____

RESPIRATORY SYSTEM

COPD/Asthma on Bronchodilators or Steroids	[__] No	[__] Yes
Chronic Intrinsic Restrictive Disease	[__] No	[__] Yes
due to: [__]Sarcoidosis [__]Fibrosis [__]Other _____		
Documented obstructive sleep apnea	[__] No	[__] Yes
Documented central sleep apnea	[__] No	[__] Yes
Other Pulm. Disease	[__] No	[__] Yes

Specify: _____

Smoker [__] Never [__] Present [__] D/C <1 year [__] D/C ≥1 year

Intubated & Ventilated Prior to Arrival to OR [__] No [__] Yes

OTHER SYSTEMS

Renal Failure on Dialysis	[__] No	[__] Yes
If yes: [__]< 1 month [__]> 1 month		
Bleeding Disorders	[__] No	[__] Yes
Heparin Induced Thrombocytopenia	[__] No	[__] Yes
Hepatic Disease*	[__] No	[__] Yes
*LFT 2x normal or jaundice or ascites		
Hypothroidism	[__] No	[__] Yes
Alcoholism*	[__]No	[__] Yes [__] Former

*EtOH related life impairment or increased EtOH tolerance or withdrawal symptoms

Other Systemic Disease _____

OTHER CONSIDERATIONS

Refused Homologous Transfusions [__] No [__] Yes

If yes: [__]Religious Motives [__]Other Reason _____

PRE-ANAESTHETIC ASSESSMENT

Where [__] Ward [__] PAU [__] Day Unit [__] CCU [__] CSICU
[__] CRC [__] Cath Lab [__] OR [__] Other _____

Seen by [__] Bourke [__] Cattran [__] Dickie [__] Dupuis
[__] Hudson [__] Hynes [__] Lambert
[__] J. Macdonald [__] B. McDonald [__] Nicholson
[__] Robblee [__] Sohmer [__] Tran [__] Wilkes
[__] Resident/Fellow _____

PREOPERATIVE MEDICATIONS

I.V. Nitroglycerine	[__] No	[__] Yes
I.V. Heparin in the last 24 hours	[__] No	[__] Yes
Low Molecular Weight Heparin in the last 24 h	[__] No	[__] Yes
Aspirin in the last 5 days	[__] No	[__] Yes
Clopidogrel (PLAVIX) in the last 5 days	[__] No	[__] Yes
Prasugrel (Effient) within last 5 days	[__] No	[__] Yes
Thrombolytics in the last 24 h	[__] No	[__] Yes
Hirudin	[__] No	[__] Yes
Beta-blocker	[__] No	[__] Yes
ACE-Inhibitor	[__] No	[__] Yes
Anti-lipid	[__] No	[__] Yes
Calcium entry blocker	[__] No	[__] Yes
I.V. Inotropes/Vasopressors	[__] No	[__] Yes
Amiodarone	[__] No	[__] Yes
Other antiarrhythmic agents	[__] No	[__] Yes
Systemic Corticosteroids	[__] No	[__] Yes
Coumadin	[__] No	[__] 5 days or less [__] > 5 days
Dabigatran (Pradax)	[__] No	[__] 5 days or less [__] > 5 days

Other Unusual Rx _____

ASA PHYSICAL STATUS

[__] I [__] II [__] III [__] IV [__] V [__] E

CARDIAC ANAESTHESIA RISK EVALUATION (CARE) SCORE

[__] I Patient with stable cardiac disease and no other medical problem. A non-complex surgery is undertaken

[__] II Patient with stable cardiac disease and one or more controlled medical problems. A non-complex surgery is undertaken

[__] III Patient with any uncontrolled medical problem OR patient in whom a complex surgery is undertaken. **(See Below)**

[__] IV Patient with any uncontrolled medical problem **AND** in whom a complex surgery is undertaken. **(See Below)**

[__] V Patient with chronic or advanced cardiac disease for whom cardiac surgery is undertaken as a last hope to save or improve life.

[__] E Emergency - as soon as diagnosis is made and OR is available.

Examples of Uncontrolled Medical Problems	Examples of Complex Surgeries
1) Renal dysfunction (creatinine >140 µmol/L)	1) Redo Sternotomy
2) Unstable angina on I.V Heparin, Low Molecular Weight Heparin or I.V. NTG.	2) Combined valve and CABG surgery
3) Preoperative IABP	3) Double or triple valve surgery
4) Heart failure with pulmonary or peripheral edema or 3rd heart sound or marked JVD	4) CABG & LV aneurysmectomy/plication
5) Pulmonary hypertension (syst. PAP >50)	5) Aortic arch surgery
6) Debilitating systemic diseases	6) Procedures requiring circulatory arrest
7) Uncontrolled hypertension (SBP >160 and/or DBP >105	7) VSD repair after myocardial infarction
8) Active endocarditis	8) Diffuse CAD requiring multiple coronary endarterectomy/stentectomy
	9) Bentall procedure
	10) Combined cardiac/aortic surgery
	11) AVR Homograft

The Emergency definition in the CARE score is only for true emergencies: These are surgeries done as soon as the diagnosis is made and as soon as the OR is available. They do not include patients with unstable angina who spend the night in CCU waiting for surgery the day after, even if within 24 h

INTRAOPERATIVE DATA

*what the case ended up being

[__] CPB Case* [__] Non-CPB Case*

INDUCTION

[__] Smooth
[__] Pre-induction insertion of IABP in OR
[__] Crash on induction (requiring CPR or Rapid Chest Opening & CPB)
[__] Bradycardia/Hypotension requiring pacing or cardiac massage

INTUBATION

[__] General Anaesthesia [__] Awake

Complications [__] None [__] Unanticipated difficult intubation
[__] Laryngeal Trauma [__] Other

Comments:_____

MONITORING

Hemodynamics [__] CVP
[__] PA Catheter **With:** [__] CCO [__] SvO_2 [__] RVEF
[__] TEE
If measured, intraoperative EF by TEE = _____%
Or visual estimate: [__]≥ 50% [__]35-49% [__]20-34% [__]<20%

Neurological [__] BIS [__] EEG [__] Transcranial Doppler

PRE-CPB PERIOD or NO-CPB CASES

Ischemia (ST or TEE or PAP Δ_s) [__] No [__] Yes

Hypotension (SBP <80 mmHg) requiring:
[__] Vasopressor Infusion* [__] Immediate CPB
*does not include bolus of ephedrine or neosynephrine

Hypertension (SBP >180 mmHg) [__] No [__] Yes

Undesired Bradycardia (HR <40/min) [__] No [__] Yes

Low CO Requiring Inotropes [__] No [__] Yes

Supraventricular Arrhythmia Requiring Rx [__] No [__] Yes

Ventricular Arrhythmia Requiring Rx [__] No [__] Yes

Respiratory Problems [__] No [__] Yes
If Yes [__] Hypoxemia [__] Severe Bronchospasm
[__] Pneumothorax [__] Hemothorax
[__] Other _____

Non-CPB Case converted to CPB Case [__] No [__] Yes

IABP inserted before CPB (Post-Induction) [__] No [__] Yes

Surgical Difficulties/Complications [__] No [__] Yes

Comments_____

CPB PERIOD

[__] Uncomplicated
[__] Heparin Resistance (ACT <400 sec after heparin ≥400 units/kg)
[__] Hypotension (MAP <40 mmHg for >5 min)
[__] Hypertension (MAP >120 mmHg for 5 min)
[__] Hypoxemia (PaO_2 <60 mmHg with FiO_2 of 1.0)
[__] Acidosis (Base Deficit >10 mmol/L)
[__] Clotting of the CPB Circuit or other Circuit Failure
[__] Circulatory Arrest with Deep Hypothermia

Surgical Difficulties/Complications [__] No [__] Yes

Comments_____

CPB WEANING (the period from weaning until protamine is started)

*Note - Ephedrine/Phenylephrine Bolus ≠ Inotropic/Vasopressor Support

[__] Easy - no Inotropic Infusion [__] Difficult (>1 attempt or >5 min)

[__] Easy - with Inotropic Infusion No. Attempts if >1 _____

Inotropic Support With
[__] Dopamine <5 µg/kg/min [__] Dopamine ≥5 µg/kg/min
[__] Dobutamine [__] Epinephrine [__] Norepinephrine
[__] Milrinone [__] Vasopressin
[__] IABP Site: [__] R Fem [__] L Fem [__] Transthoracic
[__] Assist Device: [__] LV [__] RV [__] Biventricular
[__] Other _____

POST-CPB PERIOD or END OF THE CASE IF NO CPB

Note - STABLE is defined as HR = 50 - 110/min. SBP = 90 - 130 mmHg
CI > 2 L/min/m^2, wedge < 24 mmHg and CVP < 20 mmHg

Hemodynamically [__] Stable - no Inotropic Support
[__] Stable - with Inotropic Support
[__] Unstable

Inotropes/Vasopressors used
[__] Dopamine <5 µg/kg/min [__] Dopamine ≥5 µg/kg/min
[__] Dobutamine [__] Epinephrine [__] Norepinephrine
[__] Milrinone [__] Vasopressin
[__] IABP Site: [__]R Fem [__]L Fem [__] Transthoracic
[__] Assist Device: [__]LV [__]RV [__] Biventricular
[__] Other _____

Ischemia (ST or TEE or PAP Δ_s) [__]No [__]Yes

Hypertension (SBP >180 mmHg) [__]No [__]Yes

VT/VF requiring Rx [__]No [__]Yes

Coagulopathy [__]No [__]Yes
determined by [__]Clinical Observation [__]Lab Tests

Reaction to Protamine
[__]None or Mild Hypotension
[__]Severe Hypotension
[__]Pulmonary Hypertension

Back on CPB X [__] 0 [__]1 [__] 2 [__] 3 [__] ≥4
Reason: [__] Unstable [__] Bleeding
[__] Graft/Valve Revision [__] Arrhythmias
[__] Other _____

Respiratory Problems [__] No [__] Yes
If yes: [__] Hypoxemia [__] Severe Bronchospam
[__] Pneumothorax [__] Hemothorax
[__] Other _____

Reopened before leaving OR [__]No [__]Yes
Reason: [__] Unstable [__] Bleeding
[__] Graft/Valve Revision [__] Arrhythmias
[__] Other_____

Surgical Complications [__]No [__]Yes

Comments _____
Intraoperative Death [__]No [__]Yes

INTRAOPERATIVE TRANSFUSIONS [__]No [__]Yes

Allogeneic red blood cells	# units:_____
Fresh frozen plasma	# units:_____
Platelets	# units:_____
Cryoprecipitates	# units:_____
Autologous whole blood	# units:_____
Factor VIIa	# mg: _____
Octoplex	# ml: _____

Other:_____

RECOVERY

Recovered in OR [__] No [__] Yes

Condition on Arrival to CRR/CSU

[__] Stable - no Inotropic/Vasopressor Support
[__] Stable - with Inotropic/Vasopressor Support
[__] Unstable
Note -STABLE is defined as HR = 50 - 110/min, SBP = 90 mmHg -130 mmHg
CI > 2 L/min/m^2, wedge < 24 mmHg and CVP < 20 mmHg

Case Started @ [__] Time _____:_____
[__] During Regular Weekday
[__] During Weekend/Holiday

Case Finished by Anesthetist Who Started the Case [__]No [__]Yes

If no, when: [__] Pre-CPB [__] During CPB [__] Post-CPB

Patient unstable at handover between anesthetists: [__]No [__]Yes

Uncontrolled bleeding at handover between anesthetists: [__]No [__]Yes

Appendix B: Cardiac Surgical Critical Care Database Form

CARDIAC SURGICAL CRITICAL CARE DATABASE - University of Ottawa Heart Institute

Procedure: CABG x (__), Endart of : [__]RCA [__]LAD [__] Cx
[__]MID-CAB, [__]AVR, [__]AVR/root enl, [__]AVR homograft,
[__]Bentall, [__]MVR, [__]TVR, [__]MVr, [__]TVr, [__]Ross,
[__]Transplant, [__]Thoracic Aorta, [__]ASD, Other_____

Intensivist: [__]Bourke, [__]Cattran, [__]Dupuis, [__]Macdonald
[__]McDonald, [__]Wilkes, Other_____

Date of surgery YY___/MM___/DD___ **Sex:** [__]F, [__]M **Ht:** _____cm **Wt:** _____Kg **BMI:** _____ **BSA:** _____
(2009/07/03)

Admission to CSU

	Date	Time	Diagnosis (circle one)
Initial -	YY___/MM___/DD___	_____hrs	post-op, MI, cardiogenic shock, respiratory failure, sepsis, tamponade, bleed, other_____
Other -	YY___/MM___/DD___	_____hrs	post-op, MI, cardiogenic shock, respiratory failure, sepsis, tamponade, bleed, other_____
Other -	YY___/MM___/DD___	_____hrs	post-op, MI, cardiogenic shock, respiratory failure, sepsis, tamponade, bleed, other_____

Ready for discharge from CSU

	Date	Time		Date	Time
Initial1 -	YY___/MM___/DD___	_____hrs	Other2 -	YY___/MM___/DD___	_____hrs
Other3 -	YY___/MM___/DD___	_____hrs			

Discharge from CSU

	Date	Time	Location	
Initial -	YY___/MM___/DD___	_____hrs	H3, H4, H5,CRC, CCU, OCH, Other hospital	, Other site, deceased
Other -	YY___/MM___/DD___	_____hrs	H3, H4, H5,CRC, CCU, OCH, Other hospital	, Other site, deceased
Other -	YY___/MM___/DD___	_____hrs	H3, H4, H5,CRC, CCU, OCH, Other hospital	, Other site, deceased

Extubation(s) **Reintubation(s)**

Date	Time		Date	Time	Reason
Initial - YY___/MM___/DD___	_____hrs	Initial -	YY___/MM___/DD___	_____hrs	resp,cvs,cns,sepsis, other_____
Other - YY___/MM___/DD___	_____hrs	Other -	YY___/MM___/DD___	_____hrs	resp,cvs,cns,sepsis, other_____
Other - YY___/MM___/DD___	_____hrs	Other -	YY___/MM___/DD___	_____hrs	resp,cvs,cns,sepsis, other_____

Discharge from Hospital: YY___/MM___/DD___ **Location:** H3, H4, H5, CRC, CSU, OCH, Other hospital, Other site, deceased

Deceased: no[__] / yes[__] **Deceased location:** OR, H3, H4, H5, CRC, ICU

Comments_____

CVS		**Date**	**Date resolved**
Peri-op MI	no[__] / yes[__]	YY___/MM___/DD___ ECG[__], TNT[__], TNI [__]	
Used ≥ 2 inotropes >24 hrs	no[__] / yes[__]		
Post-op low cardiac index YY___/MM___/DD___	no[__] / yes[__]	YY___/MM___/DD___	
cumulative duration:	[__] hrs		
Ventricular tachycardia	no[__] / yes[__]	YY___/MM___/DD___	
Ventricular fibrillation	no[__] / yes[__]	YY___/MM___/DD___	
Other VPB's requiring rx	no[__] / yes[__]	YY___/MM___/DD___	
Atrial Fib/flutter	no[__] / yes[__]	YY___/MM___/DD___	

Other SVT no[__] / yes[__] YY___/MM___/DD___
2nd degree HB - type I no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
2nd degree HB - type II no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
3rd degree HB no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Cardiac arrest (s) no[__] / yes[__] YY___/MM___/DD___
no[__] / yes[__] YY___/MM___/DD___
Post-operative reopening no[__] / yes[__] YY___/MM___/DD___
Site: COR[__], CRR[__], CSU[__], CRC[__], Other _____
Reason(s): tamponade[__], bleeding[__], low cardiac output[__]
Ischemia:
Cardiac no[__] / yes[__] YY___/MM___/DD___
Upper extremity no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Lower extremity no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Pulmonary artery rupture no[__] / yes[__] YY___/MM___/DD___
Other Cardiovascular
problems_____

CARDIAC SURGICAL CRITICAL CARE DATABASE - University of Ottawa Heart Institute (cont'd)

CNS		**Date**	**Date resolved**
Encephalopathy	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
Stroke/CVA -Focal Deficit	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
Site:	left hemisphere[__], right hemisphere[__], brain stem[__], other_____		
Spinal chord injury	no[__] / yes[__]	YY___/MM___/DD___	
Peripheral Neuropathy / neuropraxia	no[__] / yes[__]		
details:_____			
Polyneuropathy	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
New myopathy	no[__] / yes[__]	YY___/MM___/DD___	
Acute psychosis	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
Seizures	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
Other muscular problems:_____			

Respiratory		**Date**	**Date resolved**
Pneumothorax	no[__] / yes[__]	YY___/MM___/DD___	
ECMO	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
Subcutaneous emphysema	no[__] / yes[__]	YY___/MM___/DD___	YY___/MM___/DD___
Atelectasis	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
Cardiogenic pulmonary edema	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
ARDS	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
Pleural effusion requiring drainage	no[__] / yes[__]	YY___/MM___/DD___	

Hemothorax requiring drainage no[__] / yes[__] YY___/MM___/DD___
Pulmonary embolism no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Phrenic nerve palsy no[__] / yes[__] YY___/MM___/DD___
Site: right[__], left[__]
(Pneumonia-tracheobronchitis - see infections)
(Bronchoscopy - see procedures/interventions)
Other respiratory: _____

Gastrointestinal - hepatic **Date** **Date resolved**

Hepatocellular dysfunction no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Hepatic obstruction no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Pancreatitis no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Cholecystitis no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Ileus no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Bowel ischemia no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Upper GI bleed no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Lower GI bleed no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Gastric ulcer no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Duodenal ulcer no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Esophageal perforation no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Stomach perforation no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Duodenal perforation no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Jejunal / Ilium perforation no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Large bowel perforation no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
Other problems:_____

Hematology **Date** **Date resolved**

Coagulopathy requiring treatment no[__] / yes[__] YY___/MM___/DD___
with lab criteria [__], clinical [__]
Etiology: dilutional[__], DIC / fibrinolysis[__]
Thrombocytopenia no[__] / yes[__] YY___/MM___/DD___
Heparin induced thrombocytopenia no[__] / yes[__] YY___/MM___/DD___
Deep venous thrombosis no[__] / yes[__] YY___/MM___/DD___
Factor VIIa used post op no[__] / yes[__]
Others: _____

Renal **Date** **Date resolved**

new acute renal failure (creatinine > 150) no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
hyperkalemia (> 6 or requires Rx) no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
hypophosphatemia (< 0.5 or requires Rx) no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
hypomagnesemia (< 0.5 or requires Rx) no[__] / yes[__] YY___/MM___/DD___
YY___/MM___/DD___
hyponatremia (< 120 or requires Rx) no[__] / yes[__] YY___/MM___/DD___ YY___/MM___/DD___
metabolic alkalosis (BE > 10) no[__] / yes[__] YY___/MM___/DD___ YY___/MM___/DD___
lactic acidosis (lactate > 10) no[__] / yes[__] YY___/MM___/DD___ YY___/MM___/DD___
(dialysis - see Procedures/interventions)
other(s):_____

Infections/Inflammatory syndromes (documented & requiring treatment)

		Date	Date resolved
tracheitis/bronchitis	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
pneumonia	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
VAP	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
sinusitis	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
urinary tract infection	no[__] / yes[__]	YY___/MM___/DD___	
line infection	no[__] / yes[__]	YY___/MM___/DD___	
endocarditis	no[__] / yes[__]	YY___/MM___/DD___	
wound:			
sternal:			
superficial	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
deep	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
leg:	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
SIRS	no[__] / yes[__]	YY___/MM___/DD___	
YY___/MM___/DD___			
other(s) _____		YY___/MM___/DD___	
YY___/MM___/DD___			
_____		YY___/MM___/DD___	
YY___/MM___/DD___			
_____		YY___/MM___/DD___	
YY___/MM___/DD___			

positive cultures requiring Rx:

site(s)	organism(s)	date(s)
_____	_____	YY___/MM___/DD___
_____	_____	YY___/MM___/DD___
_____	_____	YY___/MM___/DD___
_____	_____	YY___/MM___/DD___
_____	_____	YY___/MM___/DD___
_____	_____	YY___/MM___/DD___
_____	_____	YY___/MM___/DD___
_____	_____	YY___/MM___/DD___

Procedures / Interventions **Date** **Date completed**

nutrition

parenteral nutrition:

central no[__] / yes[__] YY___/MM___/DD___ YY___/MM___/DD___

peripheral no[__] / yes[__] YY___/MM___/DD___ YY___/MM___/DD___

enteral nutrition no[__] / yes[__] YY___/MM___/DD___ YY___/MM___/DD___

Procedures / Interventions (cont'd)

Date resolved **Date**

renal

CAVH no[__] / yes[__] acute[__] /chronic[__] YY___/MM___/DD___ YY___/MM___/DD___

YY___/MM___/DD___ YY___/MM___/DD___

CVVH no[__] / yes[__] acute[__] /chronic[__] YY___/MM___/DD___ YY___/MM___/DD___

YY___/MM___/DD___ YY___/MM___/DD___

peritoneal dialysis no[__] / yes[__] acute[__] /chronic[__] YY___/MM___/DD___ YY___/MM___/DD___

YY___/MM___/DD___ YY___/MM___/DD___

hemodialysis no[__] / yes[__] acute[__] /chronic[__] YY___/MM___/DD___ YY___/MM___/DD___

YY___/MM___/DD___ YY___/MM___/DD___

YY___/MM___/DD___

cardiovascular

'post-op' IABP insertion no[__] / yes[__] YY___/MM___/DD___ YY___/MM___/DD___

'post-op' VAD insertion no[__] / yes[__] left[__], right[__] YY___/MM___/DD___ YY___/MM___/DD___

temporary pacer used:

epicardial no[__] / yes[__]

mode: AAI[__], AOO[__], VVI[__], VOO[__], DDD[__], DOO[__], other _____

transvenous no[__] / yes[__]

mode: AAI[__], AOO[__], VVI[__], VOO[__], DDD[__], DOO[__], other _____

external transthoracic no[__] / yes[__]

esophageal no[__] / yes[__]

respiratory

bronchoscopy(s) no[__] / yes[__] YY___/MM___/DD___ YY___/MM___/DD___

YY___/MM___/DD___ YY___/MM___/DD___

tracheostomy no[__] / yes[__] YY___/MM___/DD___

Nitric Oxide no[__] / yes[__] YY___/MM___/DD___

BIPAP no[__] / yes[__] YY___/MM___/DD___ YY___/MM___/DD___

Others

Pressure ulcers no[__] / yes[__] YY___/MM___/DD___

Falls	no[__] / yes[__]	YY___/MM___/DD___
	no[__] / yes[__]	YY___/MM___/DD___
	no[__] / yes[__]	YY___/MM___/DD___

other(s)_____
_____

Laboratory parameters

highest vales of:

CK	_____	YY___/MM___/DD___
	YY___/MM___/DD___	
TNT	_____	YY___/MM___/DD___
	YY___/MM___/DD___	
TNI	_____	YY___/MM___/DD___
	YY___/MM___/DD___	
Creatinine	_____	YY___/MM___/DD___
	YY___/MM___/DD___	
AST	_____	YY___/MM___/DD___
	YY___/MM___/DD___	
ALT	_____	YY___/MM___/DD___
	YY___/MM___/DD___	
GGT	_____	YY___/MM___/DD___
	YY___/MM___/DD___	
LDH	_____	YY___/MM___/DD___
Bilirubin(total)	_____	YY___/MM___/DD___
Bilirubin(direct)	_____	YY___/MM___/DD___
Lipase	_____	YY___/MM___/DD___
Potassium	_____	YY___/MM___/DD___
WBC	_____	YY___/MM___/DD___
lactate	_____	YY___/MM___/DD___

lowest values of:

Hb	_____
Phosphate	_____
Magnesium	_____
Albumin	_____
Total Protein	_____
WBC	_____
Platelet	_____

Chest tube drainage 1st 12 hrs _____ mL

Appendix C: Cardiac Surgery Database Form

Discharge Summary

Patient	DOB	Admission date _____
Number	□ M □ F	Surgery date _____
Surgeon	Refer.#	Discharge date _____

Pre-op Diagnosis: □ Coronary disease □ Valvular diease □ Aortic dissection □ Aortic aneurysm □ LV aneurysm □ Endocarditis □ Pericardial disease □ Tumor □ Cardiomyopathy □ Congenital Disease □ CTEPH □ A.fib □ Other (specify)

Clinical status □ Asymptomatic □ Symptomatic □ Cardiogenic Shock □ Multiple medical problems □ high risk □ Other (specify)
□ **Elective Surgery** □ **Urgent Surgery** □ **Emergent Surgery**

Procedure
Post-op Course □ Uncomplicated □ Complicated
Complications:
□ Reopening for □ bleeding □ tamponade □ coagulopathy □ cardiac arrest □ delayed chest closure □ other
□ Cardiac Arrest □ resuscitated
Cardiovascular
□ VT □ VF □ SVT □ A.fib/flutter □ heart block □ heart failure/pulmonary edema □ MI □ recurrent angina
□ other (specify)
Rhythm at discharge □ NSR □ A.fib □ A.flutter □ PPM implanted □ AICD implanted
Respiratory
□ Respiratory failure □ reintubation □ tracheotomy □ Pulmonary Embolus □ Hemothorax □ Pleural effusion
□ Pneumothorax □ other (specify)
CNS
□ CVA □ RIND □ TIA □ encephalopathy □ confusion □ brain damage □ other (specify)
GI
□ Upper GI bleeding □ Lower GI bleeding □ duodenal ulcer □ gastric ulcer □ bowel ischemia
□ liver dysfunction □ other (specify)
Renal
□ Renal insufficiency □ acute □ acute on CRF □ CVVH □ HD □ HD dependent at discharge □ other
Hematology
□ Coagulopathy □ thrombocytopenia □ heparin induced □ DVT □ other (specify)
Infections
□ Pneumonia □ Line sepsis □ Sepsis □ Endocarditis □ UTI □ sternal wound infection □ superficial □ deep □ arm □ leg □ mediastinitis □ osteromyelitis □ debridement □ other (specify)
Death □ intra-op □ post-op date _____ cause: _____
Other (specify)
Medications on discharge:
Location: □ home □ other hospital □ rehab □ GAU □ convalescent care
Comments:
Surgeon:

Appendix D: Instructions for Chart Reviewers with Definitions of Variables for Extraction

Instructions for Chart Reviewers

Thank-you for volunteering to do these chart reviews. Each reviewer is assigned 50 control cases. Please be aware that I will be independently reviewing 2 of your charts to calculate interobserver variability. Your excel file can be found in the R: drive of your heart institute computer. There are MRN numbers and dates of surgery (all in 2010) to help you identify the admission period we are interested in. Basically you will be looking in four files for most of the information: pre-anesthetic record, medication reconciliation form, preop ECHO report and discharge summary. Please have your chart reviews done by **January 31st 2012** at the latest. Please give me a shout with any questions you may have. Insert NA= not available

Item	**Entry**	**Which Document to Look In**	**Comments**
Preop eGFR(MDRD) Estimated GFR	mL/min	Lab Chemistry section, it's quickest if you use the filter function, usually at the bottom of the chemistry filter	Please insert NA if unavailable
Preop beta-blocker (BB)	Y or N	Preanesthetic chart, Medication Reconciliation Best Possible form for home meds	
Preop statin	Y or N	As above	
Preop digoxin	Y or N	As above	
Preop steroids	Y or N	As above	Some are filled in already, please check
Preop calcium channel blocker (CCB)	Y or N	As above	
Preop amiodarone (amio)	Yes or No	As above	Some are filled in already, please check
LVEF	% or NA	Preop TTE or TEE report. If preop unavailable, please use the intraop TEE. ECHOs must be within 12 months before surgery	Some are filled already, please check
LV systolic function	Normal,mild, moderate or severe dysfunction	As above	In cases where the LVEF are not found please insert the descriptor used by cardiologist for the LV systolic function.
Preop RV dysfunction	Mild, moderate, severe dysfunction	As above	
LA size	mm or NA	**Preop TTE report only**	Some echos from other institutions may be labelled as non-TOH reports after the admission date
iLAVol indexed LA Volume	mL/m2	**As above**	
E/a ratio	o.XX or NA	As above	
DT Deceleration time	s	As above	
Diastolic function	Mild, moderate, severe, NA	As above	These may not always be present, if listed please include
Postop afib (POAF)	Y or N	Discharge summary: complications section	Should be 'N', but please double-check this for me. If you do find a chart that **does** have **postop afib** then please send me the name so I can review that chart myself.

Appendix E: Variable Definitions

Variable	Definition	Explanation
1. Studyno	1-999	
2. age	years old	
3. old60	≥ 60 y.o	
4. old65	≥ 65 y.o	
5. old70	≥ 70 y.o	
6. old75	≥ 75 y.o	
7. old80	≥ 80 y.o	
8. sex	Female/ Male	
9. hght	height in cm	
10. wght	weight in kg	
11. obese	BMI ≥ 30	
12. nbmi	kg/sq(m^2)	
13. sxtype	cabg /valve/combo	
14. cpb	Y/N	
15. mvsx	Y/N	
16. vtype	A/M/T/P/N /C	aortic/mitral/tricuspid/pulmonary/not valve/combo
17. mi7	Y/N	myocardial infarction within 7 days of surgery
18. nyha	0/1/2/3/4	new york heart association (NHYA) heart failure grade
19. nyha0MS	0/M/S	M (mild) =1&2 S (severe) =3&4
20. redo	Yes/No	repeat sternotomy
21. pvd	Yes/No	peripheral vascular disease
22. lipid	Yes/No	hyperlipidemia
23. dm	Yes/No	diabetes mellitus
24. dmtx	I/NA/O /N/D	insulin/not applicable/oral meds/not on meds/diet
25. htn	Y/N	hypertension
26. cad	Yes/No	coronary artery disease
27. valve	Yes/No	valvular disease
28. av	Native/Prosthetic	aortic valve
29. as	Yes/No	aortic stenosis
30. ar	Yes/No	aortic regurgitation
31. mv	Native/Prosthetic	mitral valve
32. ms	Yes/No	mitral stenosis
33. mr	Yes/No	mitral regurgitation
34. mrg	0/1/2/3/4	mitral regurgitation grade
35. msg		no data
36. mvdz	0/1/2	1=mrg(1-2)or ms(mild) 2=mrg(3-4) or ms(mod/sev)
37. pr	Yes/No	pulmonary regurgitation
38. tv	Native/Prosthetic	tricuspid valve
39. ts	Yes/No	tricuspid stenosis

40. tr	Yes/No		tricuspid regurgitation
41. urgency	Elective/Urgent		
42. lm	Yes/No		left main stenosis >50%
43. rca	Yes/No		right coronary artery stenosis >50% stenosis
44. clad	Y/N		combined lad (native and graft to lad)
45. ccx	Y/N		combined circumflex (native & grafts)
46. crca	Y/N		combined rca (native & grafts)
47. lvfxn	normal/mild/moderate/severe		left ventricular function
48. rvfxn	normal/mild/moderate/severe		right ventricular function
49. lagrade	normal/mild/moderate/severe		left atrial dilatation
50. las	1/2		1=normal 2=abnormal
51. lasize	in mm		from echo where available
52. lanorm	Y/N		N>41mm or by description
53. paps	in mmHg		pulmonary artery systolic pressure
54. preophb			preop hemoglobin
55. preopcr			preop creatinine level
56. crcl	(140-age)xwght/crx72 x0.85 females		creatinine clearance
57. rf	Y/N		renal failure if crcl<60mL/min
58. cvaotcarotid	Yes/No		cerebral vascular accident other than carotid disease
59. cvacarotid	Yes/No		cerebral vascular accident due to carotid disease
60. copd	Yes/No		chronic obstructive pulmonary dz on puffers/steroids
61. restriclung	Yes/No		restrictive lung disease
62. smoke	N/C/R		nonsmoker/current/remote≥ 1year quit
63. htsh	Yes/No		hypothyroidism
64. etoh	Yes/No		ethanol use
65. asa	Yes/No		preop aspirin
66. plavix	Yes/No		preop plavix
67. Ivinotrope	Yes/No		preop intravenous inotropes
68. bb	Y/N		preop beta-blocker
69. ccb	Y/N		preop calcium channel blocker
70. digoxin	Y/N		preop digoxin
71. statin	Y/N		preop statin
72. amio	Yes/No		preop amiodarone
73. antiarrhy	Yes/No		preop antiarrhythmic
74. steroids	Yes/No		preop steroids (not puffers)
75. coumadin	Yes/No		No = >5 days/5 days or less
76. care	1/2/3/4/5		cardiac anesthesia risk evaluation score
77. deceased	Yes/No		in hospital
78. poaf	Y/N		new onset postoperative atrial fibrillation
79. death	Yes/No		in hospital
80. la41	Y/N		left atrial size >41mm

Appendix F: Approval Letter from Perioperative Database Unit Chairman

UNIVERSITY OF OTTAWA
HEART INSTITUTE
INSTITUT DE CARDIOLOGIE
DE L'UNIVERSITÉ D'OTTAWA

Dr. Diem Tran
University of Ottawa Heart Institute

Re: Protocol # to be determined yet

Clinical Prediction Rule for the Development of New Onset Postoperative Atrial Fibrillation in Cardiac Surgery Patients

September 28, 2011

Dear Diem,

Thank you for submitting you data request to the Ottawa Heart Institute Peri-Operative Database Unit. In addition to your data request submission, we have discussed the project in detail and I have reviewed you Research and Ethics Application and all provided documents.

The nature of the study and subsequent data request are consistent with the database content, the mandate of the University of Ottawa Peri-Operative Database Unit and also the talents and interest of the participants.

Your request for data is approved, pending Research and Ethics approval, and necessary information/data can then be obtained through either myself or Dr. Lily Tong, who is our data manager.

Please notify me when Research and ethics have communicated to you regarding the status of your application.

Thanks for your interest and for your initiative.

Respectfully,

Michael E. Bourke MD FRCPC
Chariman, Universty of Ottawa Peri-Operative Database Unit
Division of Cardiac Anesthesia and Peri-Operative Care
University of Ottawa Heart Institute

40, RUE RUSKIN STREET, OTTAWA, ON K1Y 4W7
T 613.761.5000 WWW.OTTAWAHEART.CA

Appendix G: UOHI Research Ethics Board Approval Letter

Ottawa Hospital Research Ethics Boards / Conseils d'éthique en recherches
725 Parkdale Avenue, Box 411, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax: 613-761-4311
http://www.ohri.ca/ohreb

November 10, 2011

Dr. Diem Tran
Division of Cardiac Anasthesia
University of Ottawa Heart Institute
40 Ruskin Street
Ottawa, ON K1Y 4W7

Dear Dr. Tran:

Re: Protocol # 2011759-01H **Clinical Prediction Rule for the Development of New Onset Postoperative Atrial Fibrillation in Cardiac Surgery Patients**

Protocol approval valid until - November 9, 2012

I am pleased to inform you that your Application for Chart Review underwent expedited review by the Human Research Ethics Board (HREB), and is approved. No changes, amendments or addenda may be made to the protocol without the HREB's review and approval.

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the HREB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Human Research Ethics Board is constituted in accordance with, and operates in compliance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; Health Canada Good Clinical Practice: Consolidated Guideline; Part C Division 5 of the Food and Drug Regulations of Health Canada; and the provisions of the Ontario Health Information Protection Act 2004 and its applicable Regulations.

Yours sincerely,

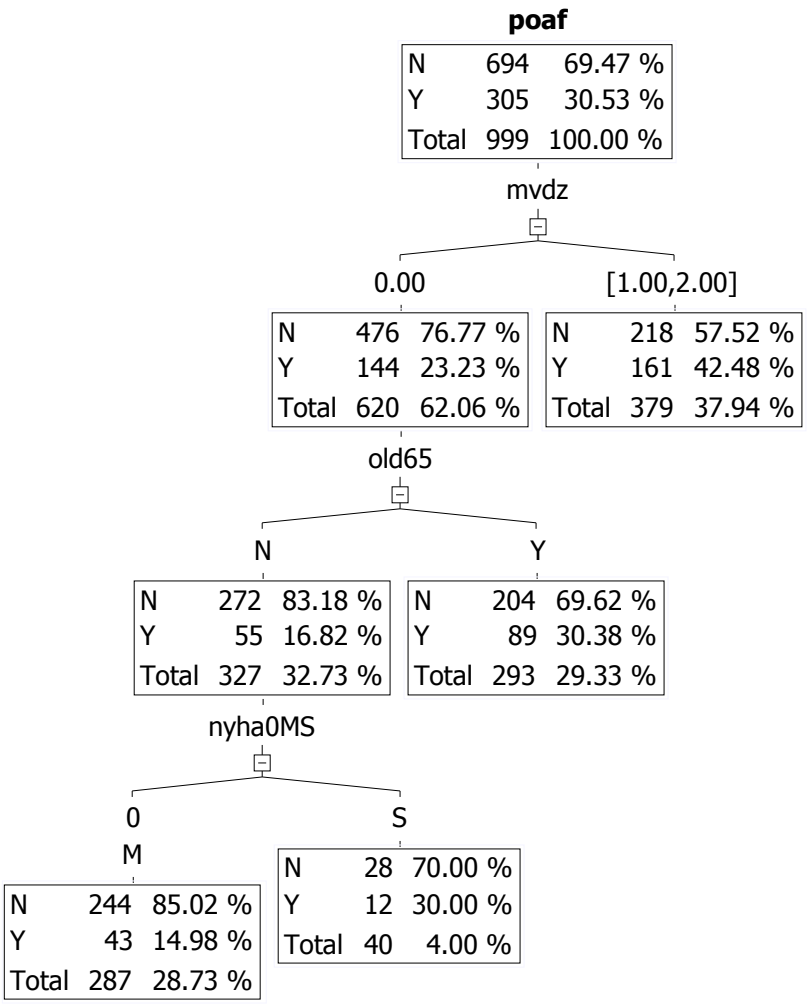
Richard F. Davies, M.D., PhD, FRCPC
Chairman
Human Research Ethics Board

/dw

Appendix H: Recursive Partitioning Models

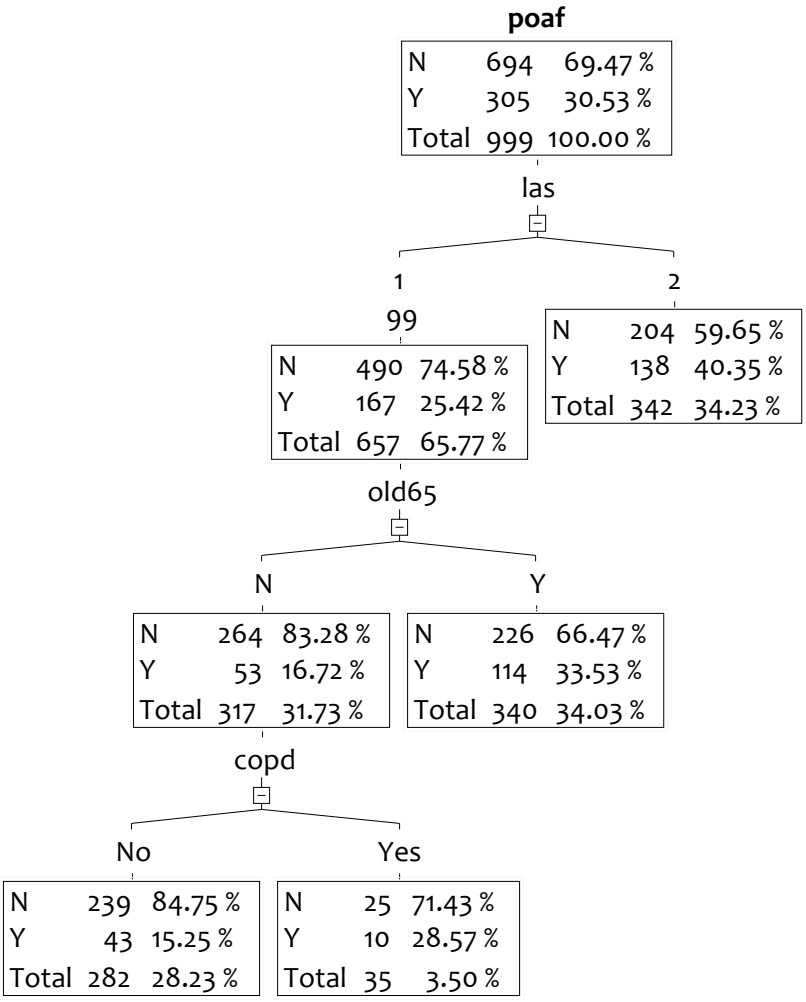
Recursive Partitioning Model #1

Variables: mitral valve disease, age ≥65 years, NYHA class



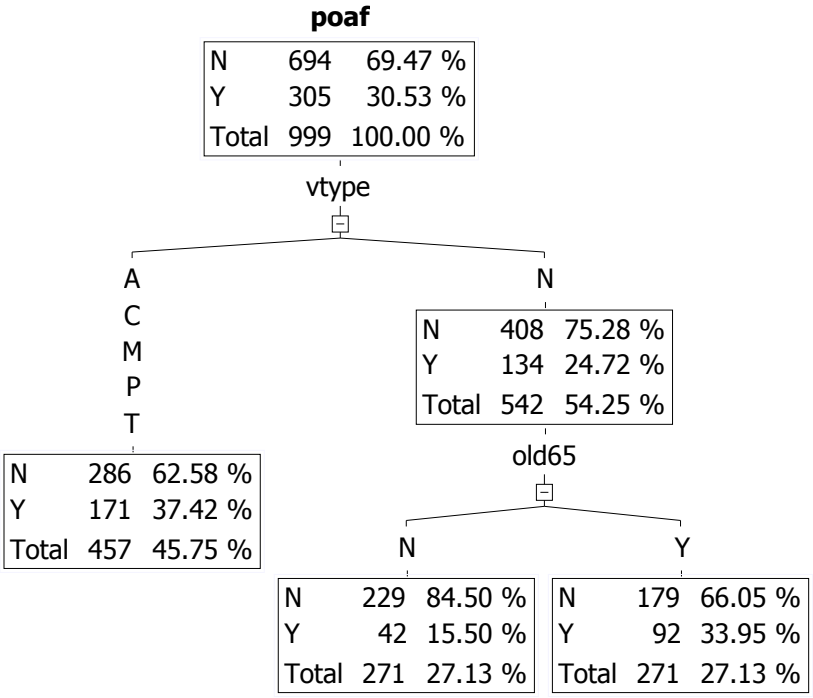
Recursive Partitioning Model #2

Variables: left atrial size, age ≥65 years, chronic obstructive pulmonary disease



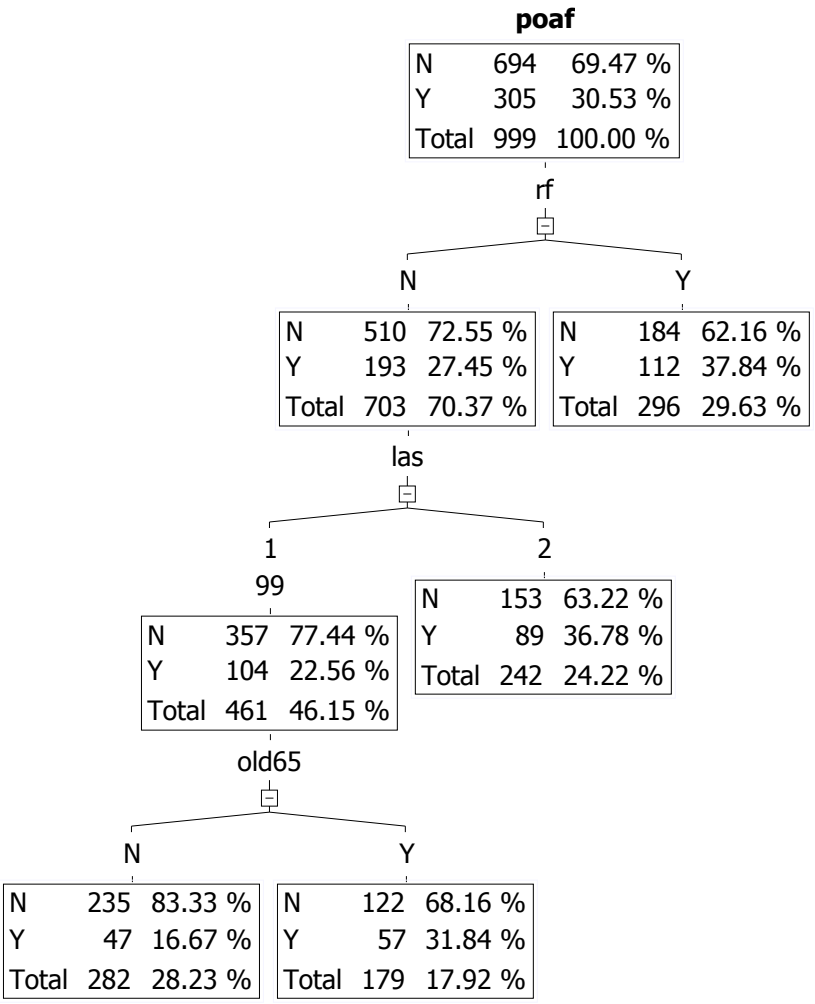
Recursive Partitioning Model #4

Variables: valve surgery, age ≥ 65 years



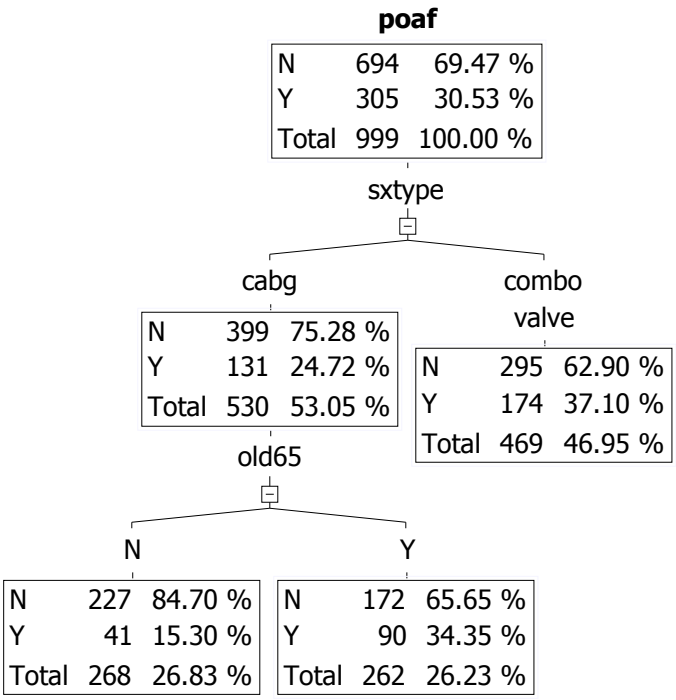
Recursive Partitioning Model #5

Variables: renal failure, left atrial size, age ≥65 years



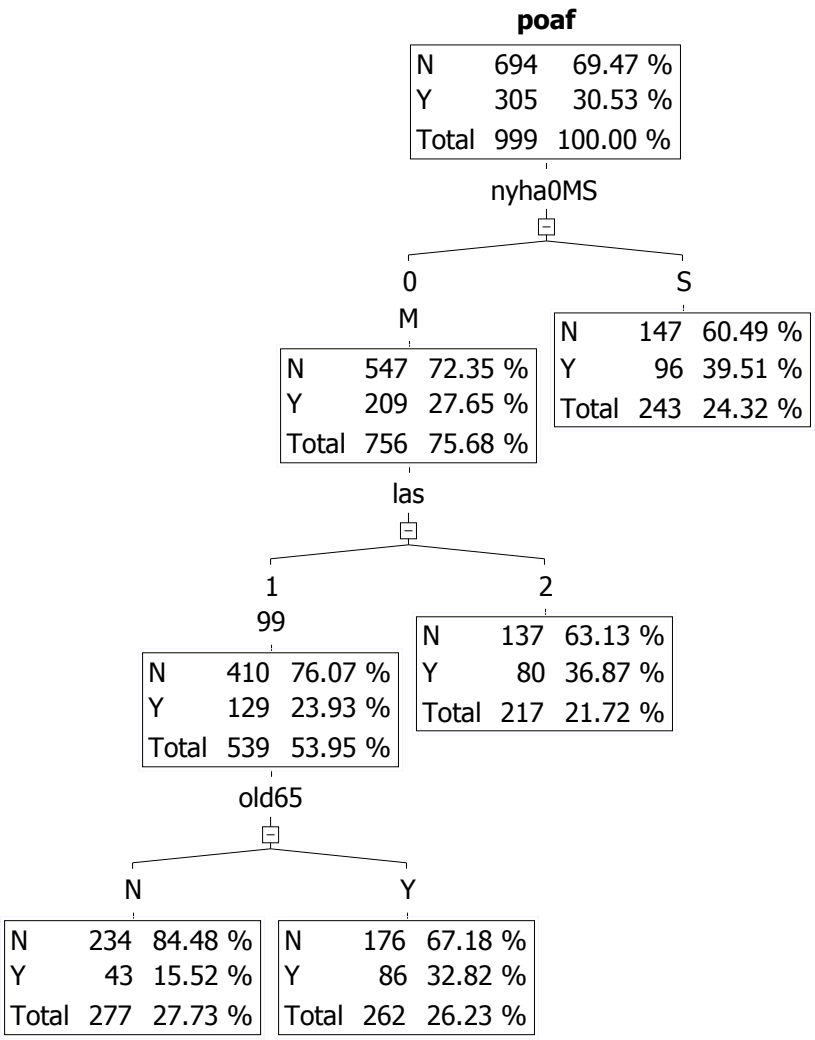
Recursive Partitioning Model #6

Variables surgery type, age ≥65 years, NYHA heart failure class



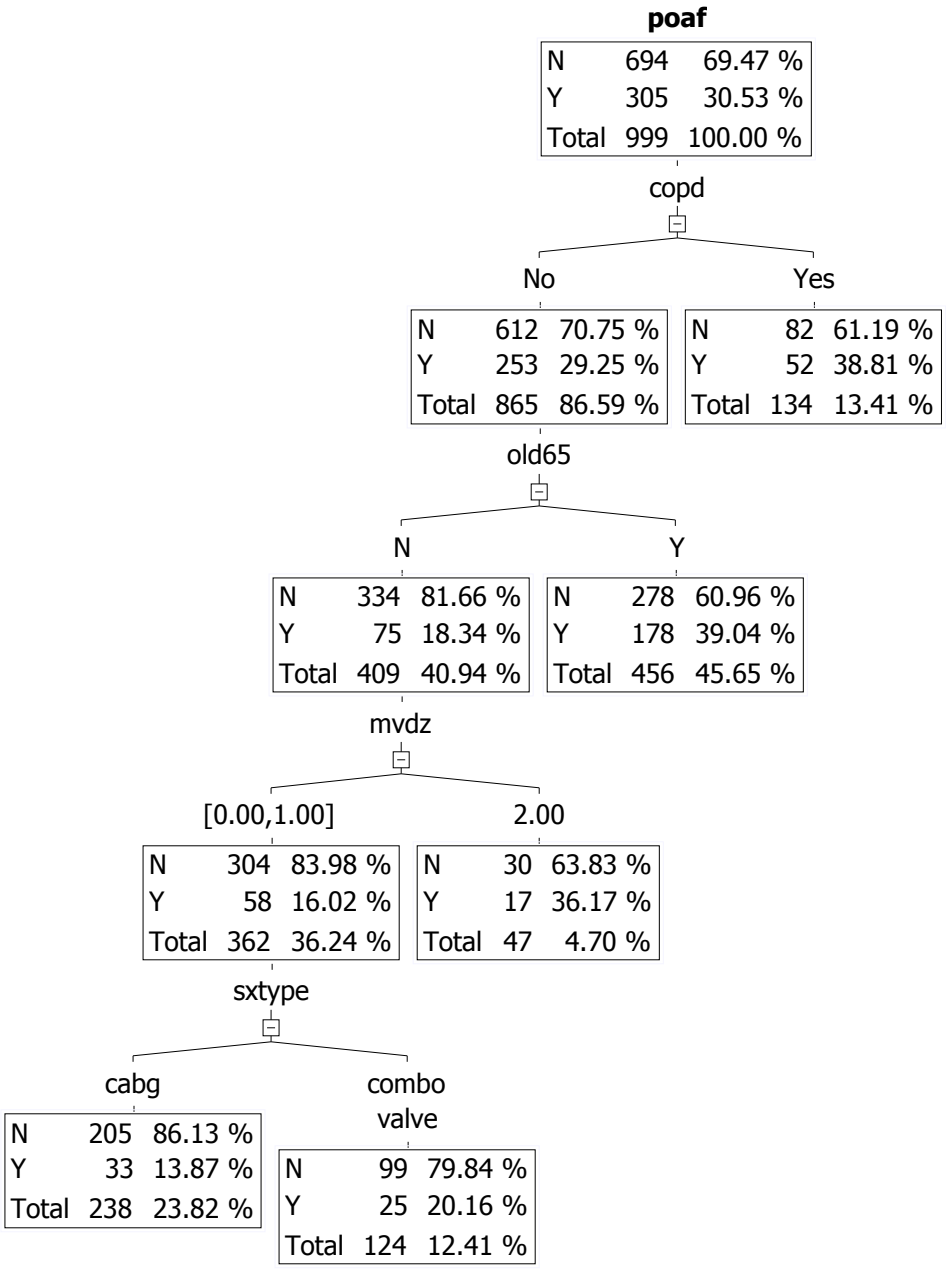
Recursive Partitioning Model #7

Variables: NYHA class heart failure, left atrial size, age≥65 years



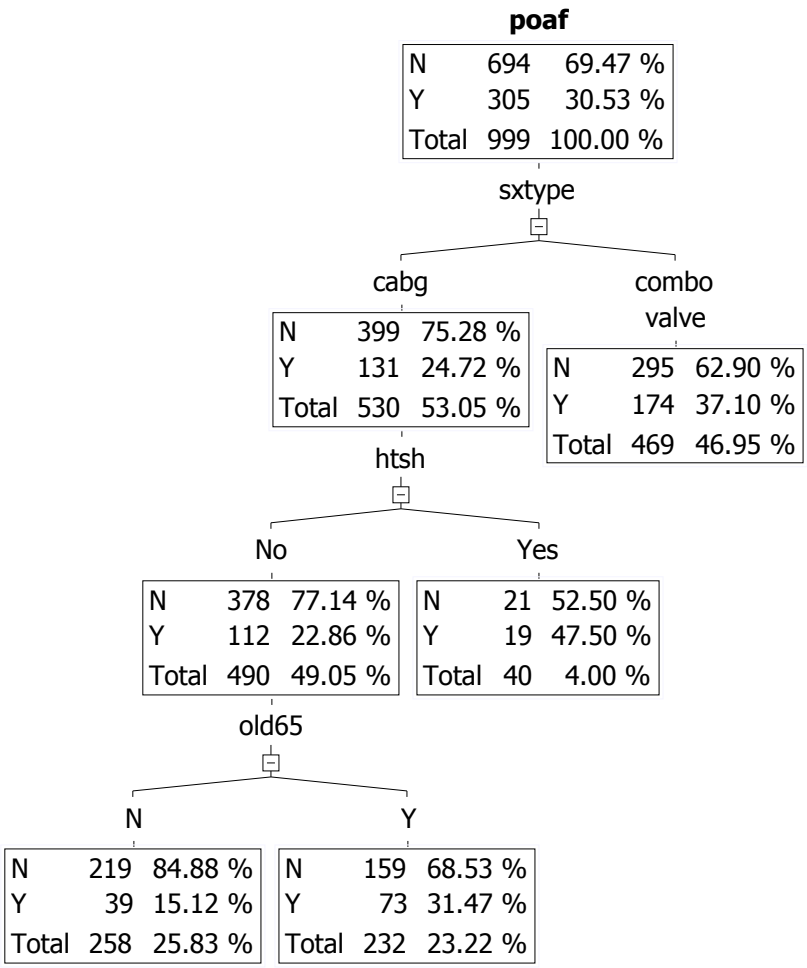
Recursive Partitioning Model #8

Variables: chronic obstructive pulmonary disease, age≥65 years, mitral valve disease



Recursive Partitioning Model #9

Variables: surgery type, hypothyroidism, age ≥65 years



Recursive Partitioning Model #10

Variables: left ventricular function, age ≥65 years, surgery type