Université d'Ottawa · University of Ottawa

EMERGENCY DEPARTMENT TREATMENT OF CLINICALLY STABLE PAROXYSMAL ATRIAL FIBRILLATION

by

ATUL KUMAR KAPUR

Thesis submitted to
the Faculty of Graduate and Postdoctoral Studies
in partial fulfilment of the requirements for the
M.Sc. degree in Epidemiology

University of Ottawa

December 2001

ABSTRACT

Introduction: Optimal management of paroxysmal atrial fibrillation (PAF), a common presenting complaint in emergency departments (EDs), remains undetermined. Methods: Six month prospective observational study at three EDs. Patients had clinically stable PAF for less than 48 hours. Conservative (rate control) and aggressive (pharmacologic and/or electrical cardioversion) treatment were analyzed. Results: 169 patients were analyzed, 32 treated conservatively and 137 aggressively. 83.9% of aggressively treated patients converted in the ED, 8.0% were admitted, and 52.3% stayed in sinus rhythm for four weeks. The corresponding proportions for conservative treatment were 34.4%, 37.5%, and 30.0%. There were 15 ED complications (2 rate control, 4 pharmacologic, and 9 electrical), two required admission (one pharmacologic and one electrical). No thromboembolism occurred by four-week follow-up. Conclusions: The results of this study – the first prospective study of ED treatment of PAF – will be used to plan a randomized controlled trial which will compare the two treatments.

ACKNOWLEDGEMENTS

When I first became interested in emergency medicine research, Dr. Terry Klassen kindled that interest and pointed me towards Ottawa and the research fellowship he and Dr. Stiell were leading. His advice, support, and encouragement were critical in starting me on the first steps of my research path, until he left for Edmonton.

My supervisors, Drs. Ian Stiell and George Wells, were instrumental in encouraging, guiding, prodding, and occasionally shoving me forward on that research path. My debt of gratitude to them cannot be adequately expressed in words, but hopefully can be paid with enough single-malt Scotch.

Melodie Mortensen, RN was diligent in finding charts and tracking patients in Ottawa. Her thoroughness made my life much easier. In Kingston, data collection was ably done by Fenni Loye and Julie Richard under the direction of Dr. Rob Brison.

The faculty and staff at the Department of Epidemiology and Community Medicine were unfailingly supportive and quick to assist whenever asked. My colleagues at The Ottawa Hospital Department of Emergency Medicine provided camaraderie, support, and time throughout my fellowship.

A special thanks goes out to my family, who have always supported me in achieving my goals and cheered me on when those goals seemed very distant.

I was personally supported during my studies by a Research Fellowship from the Emergency Health Services (EHS) Branch of the Ontario Ministry of Health and Longterm Care. The study was financially supported by research grants from the EHS Branch (Project #15200N) and from the Canadian Association of Emergency Physicians (2000 Research Grant Competition).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 INTRODUCTION

Atrial fibrillation is a cardiac arrhythmia (heart rhythm irregularity) characterized by uncoordinated atrial electrical activity, leading to lack of atrial contraction and irregular ventricular stimulation. Both of these effects contribute to the decreased cardiac function of this arrhythmia. The clinical effects range from none to palpitations to hypotension, cardiac ischemia and congestive heart failure. Atrial fibrillation can be classified as chronic (permanent or with episodes lasting more than seven days) or paroxysmal. Because of concerns of embolism, atrial fibrillation lasting longer than 48 hours is treated with three weeks of prophylactic anticoagulation before attempts are made to treat the arrhythmia. Paroxysmal atrial fibrillation of less than 48 hours duration ("Acute") is not considered to have a significant risk of embolism and, therefore, acute treatment is possible without a prophylactic course of anticoagulation.

Classically, treatment of acute paroxysmal atrial fibrillation in the emergency department has been conservative and limited to rate control and admission for definitive treatment, which usually involves measures to convert the heart back to a normal rhythm. This is similar to the treatment of chronic atrial fibrillation, which is preceded by a course of anti-coagulation. However, recognizing that this is not necessary for acute paroxysmal atrial fibrillation, some have suggested and attempted cardioversion to normal rhythm acutely, and also discharged patients from the emergency department after cardioversion. There

are, however, no prospective studies documenting the safety and efficacy of this practice. Without this evidence, many will not accept and adopt this practice.

The present study is a prospective observational study of the treatment of acute atrial fibrillation. It's goal is to determine the safety and efficacy of various treatments for acute paroxysmal atrial fibrillation and to provide data to plan a randomized controlled trial which would definitively show which is the best treatment for this condition.

2 BACKGROUND

2.1 Atrial Fibrillation

2.1.1 Definition

Atrial fibrillation is a cardiac arrhythmia (heart rhythm irregularity) characterized by disorganized atrial electrical depolarization. This uncoordinated activity causes a lack of effective atrial contraction and also leads to irregular stimulation of the atrial-ventricular node and therefore an irregular and often rapid ventricular rate.

2.1.1.1 Nomenclature

There is no universally accepted consensus on the nomenclature to use in describing the course of atrial fibrillation.[1] Arbitrarily, episodes of atrial fibrillation that spontaneously convert within seven days are called "paroxysmal" while those lasting longer than seven days are called "chronic." The seven day cutoff is arbitrary, and others have used different cutoffs.[2, 3] This classification system was created before the advent of cardioversion; if cardioversion is performed before the cutoff time limit, usually seven days, then it will not be possible to determine if the atrial fibrillation would have been paroxysmal or chronic and the terms "persistent" or "recurrent" have been used to describe this situation.[4] Other synonymous terms used include "intermittent" and "acute."[5, 6]

The first episode of atrial fibrillation is also known as "new-onset." This term may be applied to either paroxysmal or chronic atrial fibrillation as it is not possible to know what the eventual type of fibrillation will be.

In the present study, patients are only eligible if the current episode of atrial fibrillation is less than 48 hours in duration. This may include new-onset or recurrent atrial fibrillation. Since those with recurrent atrial fibrillation must have been in atrial fibrillation for less than 48 hours, then the term paroxysmal or acute is appropriate. Similarly, since paroxysmal atrial fibrillation usually precedes chronic atrial fibrillation, it is not unreasonable to use the term paroxysmal for new-onset atrial fibrillation as well. This has been done by others, as well.[7]

2.1.2 Epidemiology

Atrial fibrillation is the most common arrhythmia managed in the emergency department.[8,9] The overall population prevalence of atrial fibrillation is increasing, from 0.4% in a 1965 study to 0.89% in a 1995 review of four large population-based studies.[10, 11] This may be due to increased survival after conditions such as myocardial infarction.

The prevalence of atrial fibrillation increases with age. It is present in less than 0.1% of those younger than 40 years and 2.3% of those older than 40 years; the prevalence rises to 5.9% for those more than 65 years old. The prevalence is higher in men for all age groups.[11]

The above prevalence statistics refer to all versions of atrial fibrillation, chronic as well as paroxysmal. There are no data specifically looking at paroxysmal atrial fibrillation; however, Takahashi et al found that 40% of all those with atrial fibrillation were in

paroxysmal atrial fibrillation.[2] Using this figure and the 1995 prevalence figure above (0.89%), suggests that the overall prevalence of paroxysmal atrial fibrillation is 0.36%. The age-based prevalence figures for paroxysmal atrial fibrillation, again using the 40% proportion found by Takahashi et al, are 0.04% for those under 40 years and 0.9% for those over 40, rising to 2.4% for those over 65 years.

Michael et al identified 655 patients with acute atrial fibrillation in a database search covering 18 months at the Ottawa Civic Hospital, which had at the time 60 000 visits annually, representing 0.7% of all emergency visits.[12] By way of comparison, a review of the Ontario Health Insurance Plan database in 1999 showed that all cardiovascular diseases constituted 3.5% of all emergency department visits, endocrine disorders 0.9%, cancer and neoplasms 0.6%, and burns 0.6%.[13]

2.1.3 Clinical Effects

The lack of coordinated, effective atrial contraction with atrial fibrillation causes a decrease in ventricular filling which causes a decrease in the stroke volume of the heart and, therefore, a decrease in cardiac output. As well, the disorganized depolarization results in irregular stimulation of the atrial-ventricular node and therefore an irregular ventricular rate which is often so rapid that it does not allow adequate time between ventricular contractions for ventricular filling. Together, these two consequences of atrial fibrillation can lead to a decrease in ventricular stroke volume of 25 percent.[14]

The irregular heart rate often presents as palpitations. The decrease in cardiac output can present variously as fatigue, dyspnea, lightheadedness, cardiac ischemia and angina, or, in extreme cases, as congestive heart failure, hypotension, or decreased level of consciousness.

Takahashi et al reviewed all charts in their institution over 10 years and found 234 patients with atrial fibrillation, of whom 94 (40.2%) were described as being in paroxysmal atrial fibrillation, which they defined as fibrillation that returned to sinus rhythm without any antiarrhythmic therapy.[2] Of the 94 patients in paroxysmal atrial fibrillation, three were asymptomatic, and the most frequent symptoms in the others were palpitations, chest discomfort, breathlessness, and dizziness.

Michael et al reviewed the charts of 289 patient visits with a primary diagnosis of acute atrial fibrillation at the then Ottawa Civic Hospital over an eighteen month period.[12] They found the most frequent presenting symptom was palpitations (72% of visits), followed by chest pain (10%), shortness of breath (7%), dizziness (2%), and syncope (1%).

2.1.4 Complications and Course of Atrial Fibrillation

Complications of atrial fibrillation include angina, heart failure, and hypotension, which result from decreased cardiac output. The other major complication, thromboembolism, is felt to be due to decreased blood flow velocity in the left atrial appendage.[15, 16] Traditionally, it has been felt that 48 hours of atrial fibrillation is required before

thrombosis occurs and it is not considered a factor in treatment of acute paroxysmal atrial fibrillation. This is discussed more fully in Section 2.2.2 (below).

Takahashi et al, in their 10 year chart review of 94 paroxysmal atrial fibrillation patients, found great variability in the frequency and duration of paroxysms.[2] Nineteen subjects (20.2%) progressed to chronic atrial fibrillation. Subjects were observed for variable lengths of time and rate of progression to chronic atrial fibrillation or frequency of paroxysms were not calculated.

2.1.5 Quality of Life

Studies have shown significantly worse quality-of-life scores for patients with chronic atrial fibrillation compared to healthy individuals. The Medical Outcomes Study Short Form 36 (SF-36) reports quality-of-life on eight separately reported conceptual scales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health. These eight conceptual scales are also summarized into a physical component summary score and mental component summary score. The eight scales and two summary scores are each reported on a 0-100 scale where a higher score indicates higher quality-of-life.[17]

Jung et al reported on 175 atrial fibrillation patients and found that they scored significantly lower on the component scales of the SF-36 compared to norms for the general American population.[18] This abstract did not specify whether the patients were in

paroxysmal atrial fibrillation, but other studies have concentrated on this population. Dorian et al studied patients with at least one documented episode of intermittent atrial fibrillation, excluding those with permanent atrial fibrillation with a duration lasting longer than six months. In each component scale of the SF-36, patients with atrial fibrillation scored significantly lower than healthy people attending outpatient clinics. They found that patients with paroxysmal atrial fibrillation were as impaired as post-myocardial infarction patients.[5]

2.1.5.1 Effect of Treatment on Quality of Life

It is not clear whether rate control alone or attempted maintenance of sinus rhythm achieve significantly better return of quality of life. Hohnloser et al found, in a group with persistent atrial fibrillation, that patients whose rhythm was restored had better exercise tolerance than patients who just received rate control.[19] However, they did not show a significant difference in the three most frequently described symptoms associated with atrial fibrillation: palpitations, dyspnea, and dizziness. These symptoms are due to the same mechanism in chronic as in acute atrial fibrillation, the irregular and often too rapid heart rate. This study was unblinded and had 90% power to detect only a relatively large increase, from 50% to 70% in the proportion of patients who noted improvement in symptoms.

Bubien et al found that radiofrequency catheter ablation of the atrioventricular node and pacemaker insertion resulted in a significant increase in patient scores on all but two

component scales of the SF-36, "mental health" and "general health," and that this increase was sustained at a six-month follow-up.[20] This study was limited to patients who were referred for nodal ablation and who would presumably have had intolerable symptoms.

2.1.6 Pathophysiology

The disorganized atrial depolarization of atrial fibrillation, without effective atrial contraction, is due to multiple small re-entrant electrical circuits, or "wavelets," as opposed to the situation in normal sinus rhythm where there is regular propagation of an electrical wave which emanates from the sinus pacemaker and results in a coordinated contraction of the atrium.

The multiple wavelet hypothesis postulates that these small circuits move randomly through the atria, colliding with each other and either mutually collapsing or producing new wavelets. The number of wavelets depends on their wavelength, which is the distance traveled by the depolarization wave front during the duration of its refractory period and equals conduction velocity times refractoriness.[21] In other words, a faster wavefront increases wavelength by increasing the distance travelled in the given time (the refractory period); similarly, the longer the refractory period, the more time the wavefront has to travel. A long wavelength is less likely to be sustained in the atria since it decreases the likelihood of reentry. Short wavelengths, on the other hand, allow a greater number of

wavelets to co-exist, decreasing the likelihood that they will all extinguish simultaneously.

A common saying in medicine is "atrial fibrillation begets atrial fibrillation."[22] This means that atrial fibrillation creates the conditions which support the continuation of atrial fibrillation. Part of the reason why this condition perpetuates itself is atrial electrical remodelling.[23] This remodelling, a marked shortening of the atrial refractory period and a loss of the normal lengthening of atrial refractoriness at slower heart rates, can occur with even short episodes of atrial fibrillation. A shorter refractory period allows for wavelets with shorter wavelengths, which then increases the potential number of reentrant wavelets in the atria.[24] According to the multiple wavelet hypothesis, an increase in the number of wavelets promotes sustained atrial fibrillation. This electrical remodelling can occur quickly; shortening of atrial refractoriness has been shown to occur after 7-8 minutes of pacing-induced atrial fibrillation.[23]

2.2 Treatment of Paroxysmal Atrial Fibrillation

2.2.1 Clinical Condition

The standard of therapy for patients who are in an unstable clinical condition due to their atrial fibrillation — that is, those suffering from ischemic pain, heart failure, or hypotension — is emergent synchronized direct-current electrical cardioversion. The present study will only be considering those in a stable clinical condition. For those who

are in a stable clinical condition, treatment depends on factors such as the duration of atrial fibrillation.

2.2.2 Duration of Paroxysmal Atrial Fibrillation

Prolonged atrial fibrillation leads to ineffective atrial contraction and mechanical dysfunction of the atrium, including left atrial dilation. This results in stasis of blood in the left atrium and, subsequently, thrombus formation. Once cardioversion occurs, this thrombus may embolize. For this reason, those who have been in atrial fibrillation for greater than 48 hours, or for an unknown length of time, are routinely treated with a minimum of three weeks of oral anticoagulation (eg: warfarin) before attempts are made to convert the rhythm.[25] This anticoagulation is normally continued for four weeks after cardioversion.

Those patients who have been in atrial fibrillation for less than 48 hours (the patient population of interest in the present study) have classically been considered at minimal risk for thrombus formation and embolization. Some have questioned this assumption.

Trans-esophageal echocardiography has been shown to have extremely high sensitivity and specificity to detect atrial thrombus. Manning et al performed trans-esophageal echocardiography in 231 patients undergoing elective cardiac surgery.[26] Comparing the echocardiography results against direct visualization during surgery, they found that trans-esophageal echocardiography was 100% sensitive for finding left atrial thrombus, and

99% specific. Prevalence of atrial thrombus was 5.2% (14 patients had positive echocardiography, of whom 12 had thrombi on direct examination).

Stoddard et al performed trans-esophageal echocardiography in 143 patients with atrial fibrillation within three days of onset of atrial fibrillation; the time of onset was determined clinically by the, "abrupt onset of new or worsening persistent cardiovascular symptoms (ie: palpitations, dyspnea, angina, dizziness)."[27] The mean duration of symptoms was 1.6 days (s.d. 0.8 d) and 127 of the patients had less than two days of symptoms. Trans-esophageal echocardiography detected left atrial thrombus in 20 patients overall (14%) including 18 (14%) of those with less than two days of symptoms. However, this was a selected, higher risk group for thrombus; all had been specifically referred for transesophageal echocardiography and 17% of them had had a recent thromboembolic event.

However, the only outcomes-based clinical study that specifically examined this issue confirmed the low risk of thromboembolism. Weigner et al prospectively studied 375 patients who had atrial fibrillation that was clinically estimated (on the basis of patient symptoms, which included acute onset of palpitations, dyspnea, angina, and dizziness) to have lasted less than 48 hours.[28] Two hundred and fifty (66.7%) converted spontaneously (ie: the patient did not receive an antiarrhythmic agent other than a ventricular rate-controlling agent and also did not receive electrical cardioversion) during their hospital admission. Another 107 (28.5%) were actively cardioverted during their admission. Three

of the 357 patients who converted to sinus rhythm had a clinical thromboembolic event (0.8%). All three had converted spontaneously.

2.2.2.1 Using Symptoms to Determine Onset of Fibrillation

There is a concern among some that duration of symptoms may not be an adequate measure of duration of atrial fibrillation and may lead to the misclassification of patients who should have been anticoagulated prior to and after cardioversion.[29] Asymptomatic episodes are known to occur and may be even more common than symptomatic ones.

Page et al studied eight patients in paroxysmal atrial fibrillation with five separate 24-hour monitor recordings over one month as well as an intermittent monitor for 29 days which was activated when the patient noted symptoms.[30] They calculated that patients had a mean of 62.5 asymptomatic events of atrial fibrillation per 100 patient-days(95% CI: 40.4 - 87.3) and a mean of 5.2 symptomatic events per 100 patient-days (95% CI: 2.7 - 9.0). The ratio of 12.1 times as many asymptomatic events was significant (95% CI: 5.8-26.4) despite the fact that they studied only eight patients.

Bhandari and the Flecainide Supraventricular Tachycardia Study Group used transtelephonic electrocardiogram monitoring (TTEM) in a study of flecainide in 64 patients with more than two episodes of paroxysmal atrial fibrillation per month.[31] Subjects were to call to enroll in the study and be trained in the use of TTEM, to report symptoms, to follow-up afer symptom resolution, and to ensure proper equipment

function. They received 2375 calls, atrial fibrillation was documented in 1021, of which 112 (11.0%) reported no symptoms. Nine hundred and nine of the 1314 symptomatic calls (69.2%) had atrial fibrillation documented and another 240 (18.3%) had another arrhythmia. The authors noted that "symptomatic calls were predictive of paroxysmal atrial fibrillation or other cardiac arrhythmias in 87.4% of the patients." Takahashi et al found only three patients of 94 who were asymptomatic when their paroxysm was detected.[2]

Several studies that are discussed in more detail elsewhere in this chapter[6, 27, 28] used onset of symptoms to determine onset of episodes of atrial fibrillation. Despite the concerns mentioned above, it appears that this is the standard method of determining onset of atrial fibrillation and that this method is accepted widely in the literature.

2.2.3 Conservative Treatment Approach

There is no universally accepted treatment for patients with clinically stable paroxysmal atrial fibrillation of less than 48 hours duration. Classically, emergency department treatment of stable paroxysmal atrial fibrillation has consisted of rate control, admission for investigation (especially in those with new-onset atrial fibrillation), and possibly elective chemical cardioversion to normal sinus rhythm (the "conservative" approach).[6, 8]

Rate control is used to relieve symptoms. Hohnloser found no significant difference in symptoms between those who were converted and those who had rate control, though it

was not a large sample.[19] Studies currently underway, such as AFFIRM are evaluating a strategy to allow the patient to remain in atrial fibrillation versus one that attempts to initially cardiovert the patient and maintain sinus rhythm.[32] However, AFFIRM is not looking at patients with less than 48 hours of atrial fibrillation, the target of the present study.

The conservative approach anticipates spontaneous conversion. Danias et al examined 356 adult patients with atrial fibrillation of less than 72 hours duration, with onset defined as the onset of symptoms, who were not receiving antiarrhythmic drugs.[33] Spontaneous conversion occurred in 242 (68%) of these patients, including 213 (73%) of the 292 who presented with atrial fibrillation of less than 24 hours duration. Total duration of atrial fibrillation was less than 48 hours in 201 patients (83%). Similarly, Weigner found a spontaneous conversion rate of 66.7 percent, although they did not report how long the episodes lasted before conversion occurred.[28]

Bellandi et al reviewed 2176 patients over a six-year period.[34] They found 1393 who had at least 4 episodes of paroxysmal or persistent atrial fibrillation in the last 12 months with the episode at enrollment lasting less than 48 hours. Spontaneous cardioversion occurred in 306 of the 1393 patients (22%).

The conservative approach does not necessarily include cardioversion to sinus rhythm. If cardioversion is performed, it occurs after a period of time to allow for spontaneous conversion.

2.2.4 Aggressive Treatment Approach

Recently, the conservative approach has been questioned because the success rate of cardioversion decreases with increased duration of fibrillation. It has been suggested that early cardioversion (the "aggressive" approach) may have a higher likelihood of success and avoid complications.[35] As well, a higher rate of successful cardioversion could lead to a decreased rate of admission to hospital and decreased costs.[12] Other potential benefits to the aggressive approach include decreased length of stay in the emergency department.

However, it is not clear whether patients would benefit from cardioversion instead of rate control, nor whether there are increased complications from this aggressive approach. As well, longterm effects such as recurrence rates are unknown.

2.2.5 Pharmacologic Cardioversion

Antiarrhythmic drugs are classified according to their effect on electrical conduction inside the cells of the heart and through the heart muscle. The Vaughn-Williams Class I (eg: procainamide) and Class III (eg: amiodarone, sotalol) agents work by prolonging atrial refractoriness, which increases the wavelength and therefore decreases the number of wavelets that are sustained.[8, 29]

There is no consensus as to the best agent for pharmacologic cardioversion. Numerous antiarrhythmic drugs have been studied, including amiodarone, dofetilide, disopyramide, flecainide, ibutilide, procainamide, propafenone, quinidine, and sotalol. Unfortunately, the studies examining these drugs have examined different populations (type and duration of atrial fibrillation, comorbid conditions, inclusion of atrial flutter), with different spontaneous conversion rates and no one drug has consistently been shown to be superior.[36] All drugs are more effective with a shorter duration of atrial fibrillation.

Procainamide is the most commonly used antiarrhythmic drug for cardioversion of atrial fibrillation, with reported cardioversion in 43 to 58 percent.[37] It's major adverse effect in acute usage is hypotension.

Michael et al found complications in 9% of patients who received pharmacologic agents suffered complications, including hypotension (5.0%), bradycardia (3.3%), and atrioventricular block (0.6%), and ventricular arrhythmia (0.6%). All of these complications were transient and none resulted in admission to hospital.[12]

2.2.6 Electrical Cardioversion

Cardioversion of atrial fibrillation to normal sinus rhythm by synchronized direct current electrical shock was first performed on November 2, 1961 by Lown and colleagues, who described a 90 percent success rate in cardioverting atrial fibrillation in their series of

patients.[38, 39, 40] Similarly, Michael et al found that electrical cardioversion was successful in 89% of attempts.[12]

A brief burst of electrical current causes simultaneous depolarization of the majority of the atria, which terminates all the wavelets. The heart's sinus node, which is the normal pacer, is then able to resume normal function.[41]

Although electrical cardioversion is significantly more effective at restoring sinus rhythm than pharmacologic means, it has not been widely used as initial therapy. Whether it is because of the need for sedation or the concept of using direct-current electrical shock, there appears to be a reluctance to use electrical cardioversion. Informal discussion with cardiology colleagues shows that they feel patients suffer psychological harm from being subject to electrical shock. This is also reflected in guidelines, which are more fully discussed in Section 2.2.9 (Current Guidelines).

2.2.6.1 Dosage

For electrical cardioversion, the energy used in the initial shock is classically 100 J.[41] Joglar et al, in a study looking only at patients who were in atrial fibrillation for more than 48 hours, randomized subjects to initially receive shocks of 100, 200, or 360 J.[42] They found that the first shock was successful in 14% of the group which received 100 J, 39% of the 200 J group, and 95% of the 360 J group; the differences between the three groups were statistically significant. There were also significant differences between the three

groups in the total number of shocks received, with higher energy groups requiring fewer shocks. This study only looked at patients who were in atrial fibrillation for more than 48 hours. Since atrial fibrillation is easier to convert with a shorter duration, the results may not apply to patients with durations of atrial fibrillation of less than 48 hours,

More recent recommendations in the literature are for the initial use of 200 J and the current Advanced Cardiac Life Support guideline recommends 100 J to 200 J.[35, 43, 44] This guideline does not differentiate between acute and longer-duration atrial fibrillation when making this recommendation.

2.2.6.2 Complications

Complications of electrical cardioversion are uncommon; they include chest wall burns, dysrhythmias, hypotension, and pulmonary edema. The sedation given for the procedure may result in hypoxia.

Omran et al studied the effect of electrical cardioversion using trans-esophageal echocardiography.[45] They found shocks did not affect echocardiographic signs of atrial function. They concluded that atrial stunning was caused by the atrial fibrillation itself, and related to its duration, rather than due to the cardioversion shocks. This is confirmed by the fact that atrial dysfunction persists even after pharmacologic cardioversion.[29] Michael et al found no complications due to electrical cardioversion.[12]

2.2.7 Stepped Therapy

Some authorities recommend that, in clinically stable patients, electrical cardioversion only be used in cases where pharmacologic therapy has been unsuccessful.[41]

Golzari et al comment that, "routine pretreatment with [Vaughn-Williams] class IA or IC agents before cardioversion, although frequently proposed, has not been validated," and go on to further refer to theoretical concerns that Class I agents may increase the energy required for cardioversion.[36]

Oral et al studied ibutilide pretreatment in 100 patients, over 80% of whom were in atrial fibrillation for longer than one week (mean 117 days, standard deviation 201 days).[46] They found that ibutilide increased success of cardioversion from 72 percent to 100 percent (including 20 percent who cardioverted solely with ibutilide). Two patients who received ibutilide (3.1%) suffered sustained polymorphic ventricular tachycardia.

2.2.8 Need for Hospital Admission

Hospital admission is recommended for patients who require electrical cardioversion. This assumes that pharmacological cardioversion is attempted initially. A reduction in hospital admissions, if it can be done without adverse outcomes, would also lead to decreased resource utilization. Lown described outpatient electrical cardioversion as early as 1965.[39]

Lesser reported on 59 patients with supraventricular arrhythmias (54 or 78% with atrial fibrillation) who were electrically cardioverted on 69 occasions in an office clinic.[47] All patients received sedation with benzodiazepines preceding the cardioversion, which was successful in 64 of the 69 procedures (93%). One patient required intravenous atropine and 0.1 mg of epinephrine for persistent sinus bradycardia. None of the patients required transfer to hospital. Three patients suffered delayed effects: one was hospitalized for pulmonary edema 8 hours after cardioversion, one had peripheral embolism 24 hours after cardioversion (despite warfarin therapy) and one died 48 hours after cardioversion of unknown causes, the article suggests acute myocardial infarction.

Mulcahy et al retrospectively examined a cohort of all patients with new-onset atrial fibrillation over six years.[48] All patients with new-onset atrial fibrillation were admitted at their institution. The authors defined the admission as medically justified if the patient was hypotensive in the emergency department, had an additional condition in the emergency department that warranted admission, or had a significant complication in the emergency department or during the admission. Of the 229 patients admitted, 143 (66%) were deemed to be medically justified and in 140 of those cases (98%), the justification for admission was apparent in the emergency department. The authors concluded that one third of their patient population could have been safely treated as outpatients and that they were identifiable in the emergency department.

Michael et al found that 280 of 289 patients were discharged home (97%).[12] This included all patients who were successfully cardioverted or received no treatment, 46 of 54 (85.2%) of those in whom cardioversion was not attempted or was unsuccessful, and 37 of 38 (97.4%) of those who spontaneously converted. One patient, who spontaneously converted, had an embolic complication. Sixty-four percent had return visits to the emergency department, with no treatment complication noted.

2.2.9 Current Guidelines

Some reviews cite spontaneous conversion rates of 70% to 80% in the first 24 hours and discourage acute cardioversion or say that cardioversion may be considered but do not actually recommend it.[9, 37]

Those who do recommend an aggressive approach have not agreed on the best method of cardioversion. Standard practice has been to attempt pharmacologic cardioversion, with one of a variety of agents.[9, 35] It has been suggested that electrical cardioversion be limited to those patients who do not revert to a sinus rhythm with pharmacologic treatment.[8, 15, 49, 50]

In 1996, the Canadian Cardiovascular Society published the results of a Consensus Conference on Atrial Fibrillation. This Conference made a recommendation that electrical cardioversion be reserved for cases where pharmacological cardioversion has failed although it also made another recommendation that electrical cardioversion may be

utilized initially. Both of these recommendations were Grade C (based on non-randomized trials with contemporaneous or historical controls or case series).[35] This consensus conference, as well as the other guidelines mentioned below, only discussed the matter of duration of atrial fibrillation in relation to the issue of pre-treatment with a course of anticoagulation; they did not suggest different treatments based on whether the fibrillation had been present for more or less than 48 hours.

The 2000 Guidelines for Emergency Cardiac Care state that "electrical cardioversion is the technique of choice for cardioversion of patients with AF to sinus rhythm.[16] Pharmacological cardioversion is recommended if electrical cardioversion is not feasible or desirable or is unsuccessful in maintaining sinus rhythm." In patients with normal cardiac function, ibutilide , flecainide, propafenone, procainamide, amiodarone, are all considered Class IIa ("acceptable, safe, and useful. • Considered standard of care: reasonably prudent physicians can choose • Considered intervention of choice by majority of experts").

The American College of Cardiology, American Heart Association, and European Society of Cardiology created a committee of experts to establish guidelines on management of atrial fibrillation.[51] They make a Class I recommendation ("general agreement that the procedure is useful and effective") for cardioversion in stable patients when symptoms are unacceptable. They make Class IIa recommendations ("weight of opinion is in favor of the procedure") for cardioversion in first-detected episodes of atrial fibrillation and for

electrical cardioversion in patients with persistent atrial fibrillation when early recurrence is unlikely. Pharmacologic cardioversion in the latter situation is a Class IIb recommendation ("usefulness/efficacy is less well established"), as is cardioversion without trans-esophageal echocardiography in the first 48 hours after onset of atrial fibrillation (in which case the committee states that anticoagulation is optional before and after cardioversion). For all of these recommendations, the level of evidence is C ("expert consensus").

Many guidelines refer to the need for admission for patients, especially for those with first-time atrial fibrillation or those who require electrical cardioversion. Falk states that in new onset atrial fibrillation, admission is only required in those with hemodynamic compromise or severely symptomatic arrhythmia, those at high risk for thromboembolism, and those in whom early cardioversion is considered.[52]

The Sixth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy accepted that patients with atrial fibrillation of less than 48 hours duration do not need prolonged warfarin prior to cardioversion. However, they added that, "It may be prudent to initiate heparin anticoagulation at presentation."[25]

2.2.10 Local Practice

The lack of consensus evident in the guidelines is reflected in local practice. Emergency physicians at the Civic Campus of The Ottawa Hospital have adopted the aggressive

approach, while those at the General Campus, as well as those at the Kingston General Hospital, have been using use the conservative approach.

There is similarly no local consensus on whether primary electrical or pharmacologic cardioversion (with electrical cardioversion used for pharmacologic treatment failures) is the safer and more effective therapy. Pharmacologic cardioversion requires close monitoring and extended observation, which leads to increased patient length of stay in the emergency department. Thus, data showing similar safety and efficacy of pharmacologic and electrical cardioversion may lead to an increased use of electrical cardioversion and therefore a decrease in average length of stay and resource utilization in emergency departments.

2.3 Summary and Rationale for Present Study

Paroxysmal atrial fibrillation is a frequent cause of emergency department visits, usually due to symptoms such as palpitations, chest pain, dyspnea, and dizziness. Despite some theoretical concerns about determining the time of onset of atrial fibrillation and the exact risk of thromboembolism, it is generally accepted that episodes of atrial fibrillation of less than 48 hours duration may be treated in the emergency department without prior anticoagulation. The literature also supports outpatient management of most cases of atrial fibrillation. However, there is no consensus, in the literature or among local emergency physicians, as to the optimal treatment approach.

Treatment of this condition usually falls into one of two approaches. Those advocating the conservative approach point to the high spontaneous conversion rate of paroxysmal atrial fibrillation of less than 48 hours duration, as well as the theoretical risks and complications of aggressive treatment. Those advocating an aggressive approach indicate it's greater success at conversion as well as the benefits of fewer hospital admissions.

Discussions with emergency physicians at The Ottawa Hospital indicate that they are each convinced that their own individual approach to the treatment of atrial fibrillation (whether conservative or aggressive) is better for patients; this reflects the lack of consensus in the literature. These physicians would not be willing to enrol their patients into a randomized trial without data showing the efficacy and safety of aggressive and conservative approaches towards treatment of paroxysmal atrial fibrillation in the emergency department. This data is not currently available in the medical literature. Therefore, a randomized trial is premature at this time, and a study to prospectively collect this data is a useful addition to the scientific knowledge on this topic.

The present study was designed to prospectively obtain this information on the efficacy and safety of the treatment approaches; the data obtained will be important to design a randomized controlled trial which would provide definitive data on a comparison of conservative versus aggressive treatment.

3 GOAL AND OBJECTIVES

3.1 Goal

The present study is a necessary step in the process leading to the overall goal. The overall goal of this research project is to determine the safest and most effective treatment for patients presenting to the emergency department in paroxysmal atrial fibrillation, in order to allow emergency physicians to provide the best care for patients with this condition.

The goal of the present study is to determine the proportion of patients treated with each approach who converted to sinus rhythm and the proportion suffering adverse effects. This will provide information necessary for planning of a randomized controlled trial which will compare the two treatment approaches.

3.2 Objectives

1) To prospectively estimate the efficacy of

    a) conservative (rate control); or

    b) aggressive (pharmacologic or electrical cardioversion)

    treatment of paroxysmal atrial fibrillation. Efficacy is defined in terms of the proportion of patients who are in a sinus rhythm at emergency department discharge or at four week follow-up.

2) To prospectively estimate the proportion of patients treated

a) conservatively; or

b) aggressively

who experience immediate or short-term (within four weeks) complications related to emergency department treatment of paroxysmal atrial fibrillation.

3) To determine the enrollment rate and follow-up rate that would be expected in a randomized controlled trial comparing different treatments for paroxysmal atrial fibrillation.

4) To determine the ease of use and comprehensiveness of data collection procedures used for the patient's emergency department visit and follow-up interview.

5) To provide a descriptive profile of the patients presenting to the emergency department with paroxysmal atrial fibrillation.

6) To describe the clinical course of paroxysmal atrial fibrillation patients.

7) To determine patients' quality of life.

4 METHODS

4.1 Patient Population

The study population of interest was patients presenting with paroxysmal atrial fibrillation of less than 48 hours duration, who were eligible for acute treatment in the emergency department.

4.1.1 Inclusion Criteria

The chart of every patient who presented to the emergency department of a participating hospital was reviewed and those who were found to be in paroxysmal atrial fibrillation were eligible, whether or not atrial fibrillation was the presenting complaint or the primary final diagnosis. Atrial fibrillation was determined by the treating physician's interpretation of a standard 12-lead electrocardiogram and did not depend on clinical symptoms or signs. The paroxysmal nature of the atrial fibrillation, defined earlier as atrial fibrillation of less than 48 hours duration, was determined by the patient's report of time of onset. Patients with either new-onset paroxysmal atrial fibrillation or with a previous history of the condition (no matter how treated or whether the treatment was successful) were eligible. Patients who were referred to the participating emergency department or who presented directly were both eligible for this study.

4.1.2 Exclusion Criteria

Because this study serves as a feasibility study for a randomized, controlled trial, the exclusion criteria (and inclusion criteria) were the same as for the anticipated trial; this

allows for the estimation of the anticipated enrollment rate in the future trial. The specific reason(s) for exclusion were recorded in order to determine each criterion's effect on recruitment.

Patients were excluded if they met any of the following criteria:

a) Patients under eighteen years of age, as this is a study of paroxysmal atrial fibrillation in adults. The condition is rare in children and treatment for this patient group would likely not be applicable to adults.

b) Patients who were previously enrolled in this study. Entering them in the study more than once would complicate the results as they would likely be treated with the same treatment that proved successful for them in the past.

c) Patients whose current episode of atrial fibrillation had started more than 48 hours before presentation to the emergency department or who were not certain when the current episode began. The definition of paroxysmal atrial fibrillation being used in this study excludes this population. Because of the increased risk of embolism of atrial thrombus after 48 hours of atrial fibrillation, there is a consensus that these patients should be pre-treated with anticoagulation for three weeks before elective cardioversion is attempted.

d) Patients whose ED record included any mention that they were pregnant, because of the unknown effects of some of the study drugs on the fetus.

e) Patients who were allergic to any of the drugs used for treatment of atrial fibrillation (rate control and/or cardioversion) or for sedation during electrical cardioversion. These allergies would affect the treatment approach chosen.

f) Patients who, in the judgement of the treating physician, were in an unstable clinical condition and required immediate synchronized electrical cardioversion on an emergent basis. "Unstable clinical condition" was defined as a patient meeting any of the criteria of having ischemic cardiac pain, being in pulmonary edema, or having a systolic blood pressure <90 mm Hg. Chest pain which was not felt to be due to acute ischemia was not a criterion for exclusion.

4.1.3 Ethical Review

Approval was received from The Ottawa Hospital's research ethics committee (Appendix A). The committee did not require consent for the review of the treatment; the study did not affect in any way the treatment delivered by the physician. A notice (Appendix B) was available in the emergency department, which the treating physician could give to the patient, informing the patient of the study and that the patient could expect a followup phone call. At the time of the followup phone call, an explanation of the study was given and verbal consent was obtained by the research nurse for the structured interview.

A somewhat different procedure was mandated by the Kingston General Hospital's research ethics committee. During the hours that a research nurse was present in the emergency department, written informed consent was obtained by the nurse. When the

research nurse was not present, a letter was sent to the patient informing them of the study and requesting consent for a follow-up interview.

4.2 Study Locations

The study took place in three locations: the full-service emergency departments at The Ottawa Hospital's Civic and General Campuses and the emergency department of the Kingston General Hospital. At the beginning of the study, the emergency physicians at the Civic Campus generally followed the aggressive treatment approach while those at the General Campus and the Kingston General Hospital generally followed the conservative approach.

The Kingston General Hospital has the only full-service 24-hour emergency department in that city; because of the equipment and facilities required to treat atrial fibrillation, this department is expected to receive all the patients in the catchment area who would present with atrial fibrillation.

In Ottawa, The Ottawa Hospital has two of the city's four full-service 24-hour emergency departments. Both hospitals are tertiary care institutions, although the emergency departments see patients presenting directly as well as those referred to the hospital. In the financial year before the study (April 1, 2000 to March 31, 2001) the General Campus Emergency Department had 54, 222 patient encounters and the Civic Campus 57, 223.

Because of its connection to the Ottawa Heart Institute, many patients with perceived cardiac symptoms (such as palpitations, which would be expected with atrial fibrillation) self-triage to the Civic Campus; there is no way for patients to present themselves to the Heart Institute directly. Because of the equipment and facilities required to treat atrial fibrillation, patients with perceived cardiac symptoms are unlikely to present to either of the Urgent Care Clinics in the city; if they do present there, they would generally be referred to one of the two participating emergency departments for treatment.

All three emergency departments are staffed on a 24 hour basis by emergency physicians, the majority of whom are certified in Emergency Medicine, either through the College of Family Physicians of Canada or the Royal College of Physicians and Surgeons of Canada. As teaching departments whose hospitals are affiliated with their local medical school, they all have residents (emergency medicine and off-service) and medical students working in the departments regularly.

4.3 Data Collection

4.3.1 Nurse-Completed Form

It was decided not to ask the emergency physicians to fill out a form at the time of the emergency visit. Most of the information required is routinely collected by the nurses or physicians and would normally be recorded, either on the triage or nursing notes or the chart itself. It was anticipated that the only information which may be missed regularly

would be the past medical history other than past atrial fibrillation. In an ongoing study, the Canadian C-Spine and CT Head study, 28% of eligible patients did not have a form filled out by the treating physician; the proportion of forms not completed on eligible patients ranged from 9% to 33% at the three sites involved in the present study (I. Stiell, personal communication). The information that would not be recorded due to the physician not completing a form at the time of treatment was determined to be less important than the information which would have been missed had the physician not completed the form.

4.3.1.1 Data Collection Procedure at The Ottawa Hospital

At the two campuses of The Ottawa Hospital, a research nurse reviewed the chart of every patient presenting to the emergency departments during the data collection period and selected those who were diagnosed with atrial fibrillation. Data from the chart, including the physician's notes as well as the nursing notes and laboratory reports, were abstracted onto the data collection form (see Section 4.3.2 below and Appendix C). Contact information for the patient (address and phone number) was also collected at this time, including alternative phone numbers, such as work or cellphone, and alternative contact persons.

Four weeks after the emergency department visit, the research nurse telephoned the patient. If there was no answer, attempts were repeated and alternative contact persons were contacted in order to ascertain other methods of contacting the subject.

Once the research nurse contacted the subject, she verbally explained the purpose of the phone call and, after answering any of the subject's questions, obtained verbal consent for the interview. After obtaining the consent, a structured interview (Appendix D) was conducted. During this interview, the nurse asked whether the patient had made and kept a follow-up appointment following the emergency department visit. Information about any treatment received and medications prescribed during that appointment was also obtained. Similar information was requested for physician's visits for recurrence of atrial fibrillation or any other reason. Patients were asked whether atrial fibrillation had recurred and whether they had any symptoms. Finally, the SF-36 quality-of-life questionnaire was administered by interview (see Section 4.3.3).

4.3.1.2 Data Collection Procedure at the Kingston General Hospital

At the Kingston General Hospital, during the hours when one of the research nurses was on duty, patients were approached by the research nurse during their emergency department visit. After written consent was obtained, the patient history information was obtained by direct interview. Information on treatment and disposition was obtained during the patient's visit. Information on patients who presented outside of the research nurses' duty-hours was obtained in a manner similar to that for Ottawa Hospital patients. Again, the structured follow-up interview was conducted over the telephone four weeks after the emergency department visit.

4.3.2 Emergency Visit

The data collection form was designed to gather information necessary to meet the objectives of this study and to include characteristics that have been found in previous studies to affect the outcome of successful cardioversion, as well as complications that were identified in previous studies (see Table 1 and Appendix C).

Initial information gathered included age, sex, hospital visited, date of visit, and treating physician. Initial vital signs were recorded, then inclusion and exclusion criteria were recorded. If the patient met any exclusion criterion, no further data were recorded.

Further information before treatment included time of triage assessment and time of emergency physician assessment. There was a spot to record whether the patient had a past history of atrial fibrillation and, if so, whether it had been successfully treated and the previous successful method(s). As well, other past medical history was also recorded for conditions which may affect atrial fibrillation (coronary artery disease, valvular heart disease, hypertension, cerebrovascular accident, diabetes mellitus, thyroid disease, thromboembolic disease, congestive heart failure) with a spot to record other past medical history. Current medications were also recorded.

Information was recorded on whether rate control was attempted. Medications given, along with route and dose given, were recorded. Also recorded were complications which occurred following rate control attempt. Specific complications related to the treatment

Table 1. Information collected regarding patients' emergency visits.

- Demographic Information
  - Age
  - Sex
  - Date of visit
  - Physician
  - Hospital
- Vital Signs
  - Heart rate
  - Respiratory rate
  - Blood pressure
- Inclusion / Exclusion Criteria
  - Atrial fibrillation
  - Under 18 years old
  - Previously enrolled in study
  - Pregnant
  - Allergic to study medications
  - Unstable clinical condition
  - Duration unknown or > 48 hours
- Times
  - Triage time
  - Time seen by emergency physician
  - Disposition time
- Past history of atrial fibrillation
  - Past history of successful treatment
- Duration of current episode
- Current medications
- Past medical history
- Rate control
  - Specific drug, route, and amount
    - Diltiazem
    - Verapamil
    - Beta-blocker
    - Other
  - Complications
    - Hypotension
    - Allergic reaction
    - Bradycardia
    - Atrioventricular block
    - Ventricular arrhythmia
    - Other
- Spontaneous conversion
- Pharmacologic cardioversion
  - Specific drug, route, and amount
    - Procainamide
    - Other
  - Complications
    - Hypotension
    - Allergic reaction
    - Bradycardia
    - Atrioventricular block
    - Ventricular arrhythmia
    - Widening of QRS complex
    - Other
  - Full dose given
  - Successful
- Electrical cardioversion attempts
  - Sedation drug, route, and amount
  - Complications of sedation
    - Hypotension
    - Allergic reaction
    - Bradycardia
    - Atrioventricular block
    - Ventricular arrhythmia
    - Hypoxia
    - Apnea
    - Other
  - Energy level of each attempt
  - Attempt successful
  - Complications from attempt
    - Hypotension
    - Allergic reaction
    - Bradycardia
    - Atrioventricular block
    - Ventricular arrhythmia
    - Thromboembolism
    - Other
- Post-procedure tests and results
  - Cardiac enzymes
  - Post-cardioversion ECG
- Emergency department consultations
- Admission to hospital
- Outpatient consultations advised

were recorded (hypotension, allergic reaction, bradycardia below 60 beats per minute, atrio-ventricular block, ventricular arrhythmia) as well as other complications. Spontaneous cardioversion was defined as the return to sinus rhythm without the use of pharmacologic or electrical cardioversion and was recorded on the data collection form. If the patient was given no treatment or only given rate control and no other treatment for longer than 30 minutes, this was considered conservative management.

Information was recorded as to whether the patient received any pharmacologic cardioversion agent, such as procainamide, including the route and dose of the medication. Specific complications were recorded including those specified above as well as widening of the QRS interval on the electrocardiogram, since it is a known adverse effect of procainamide. Information was recorded as to whether the full dose was given to the patient and whether the patient's rhythm converted to sinus rhythm.

Note was made as to whether electrical cardioversion was attempted. Sedation agents used, route, and dose were recorded, as well as any complications related to the agents (hypotension, allergic reaction, bradycardia below 60 beats per minute, atrio-ventricular block, ventricular arrhythmia, hypoxia, apnea). Details were recorded of the attempts at cardioversion, including the dose(s) used, any complications, including those above as well as thromboembolism, and whether cardioversion was successful.

Enzyme markers of cardiac injury (creatine kinase, MB fraction of creatine kinase, and/or Troponin T) and electrocardiograms were recorded if ordered along with their results. Any consultations from the emergency department were recorded, along with patient disposition (discharge or admission). Time of disposition was recorded. If the patient was not admitted, any outpatient consultations that were ordered or advised were recorded.

4.3.3 Four-week Follow-up Interview

At the four-week follow-up interview, information was recorded as to whether the patient had been given or made an outpatient appointment, whether they kept the appointment, and, if so, whether they received any treatment or were given a prescription. They were asked whether they had a recurrence of their atrial fibrillation, and whether they saw a physician for this recurrence. Again, information was gathered regarding whether any treatment was received and whether any prescription was given. Similar information was gathered for any physician visit. Subjects were also asked whether they had any symptoms since their emergency visit, specifically palpitations, lightheadedness, shortness of breath, fatigue, chest pain, loss of consciousness or stroke. They were informed that a trial comparing two methods of treatment for atrial fibrillation was being contemplated and were asked whether they would be willing to participate in such a trial.

As part of this interview, a quality-of-life questionnaire was also administered. The SF-36 is a commonly used, previously validated quality of life instrument. It provides results as two component scores (physical and mental), which themselves are based on eight

different (and separately reported) concepts: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health, as well as reported health transition over the last four weeks. There is no validated disease-specific quality-of-life instrument for paroxysmal atrial fibrillation, though studies are presently underway to evaluate some such instruments.[5, 32, 53] Other general quality-of-life instruments, such as the Health Utilities Index (HUI) were considered but the SF-36 was felt to be superior at detecting small changes in quality-of-life and has been used in other studies examining atrial fibrillation.

4.4 Data Analysis

The information from the data collection forms was entered into a SAS database at the Clinical Epidemiology Unit of the Loeb Research Institute. The cover sheet with the identifying contact information was then removed and destroyed.

The subjects were initially analyzed using descriptive methods. The demographic information, vital signs, past history of atrial fibrillation, other past history, and duration of the current episode of atrial fibrillation were reported in terms of percent, mean and standard deviation with 95% confidence intervals (for parametric variables) or median and interquartile ranges (for non-parametric). The same methods will be used to report rate of enrollment of subjects into the study, proportion of data collection forms with complete information, proportion of subjects lost to follow-up, and proportion of subjects

who refuse consent. The proportion of subjects who suffered complications, proportion who were in sinus rhythm on discharge from the emergency department, proportion who had consultations, were admitted, received further treatment after discharge, and who were still in sinus rhythm at four-week follow-up were reported using mean and standard deviation, with 95% confidence intervals. Patient length of stay in the emergency department and time from seeing the emergency physician to disposition time were reported in terms of median and interquartile range. The component summary scores and underlying scales of the SF-36 were reported as mean with standard deviation.

4.4.1 Exploratory Comparison of Aggressive and Conservative Treatment Groups

For the purpose of hypothesis-generation, the aggressive and conservative treatment groups were compared using Chi-squared for proportions and Student's t-test for normally distributed variables such as the component summary scores for the SF-36, assuming independent samples and with a p value of less than 0.05 considered significant.

4.5 Sample Size

Sample size was based on a feasible time frame of six months. The expected enrollment size was based on Michael et al's health records review of the (then) Ottawa Civic Hospital from July 1, 1995 to December 31, 1996; over this eighteen month period, 655 patients would have been considered for the proposed study.[12] Anticipated enrollment from the General Campus of the Ottawa Hospital and the Kingston General Hospital were

based on review of the databases of emergency department patients at both hospitals. Allowing for a loss to follow-up or non-completion of 10%, it was anticipated that 280 patients would be enrolled during the study period. Since the purpose of the present study was to provide information for the planning of a randomized trial, the anticipated precision of the outcome values was calculated. With a sample size of 280, the anticipated 95% confidence interval for a prevalence of 50% (which would provide the widest confidence intervals) would be ± 5.8%.

4.6 Study Funding

Peer-reviewed funding was granted by the Canadian Association of Emergency Physicians, through their 2000 CAEP Research Grants Competition, and the Emergency Health Services Branch of the Ontario Ministry of Health and Long-Term Care (Project #15200N). As well, the candidate was supported by an Emergency Health Services Research Fellowship, also from the Ontario Ministry of Health and Long-Term Care.

5 RESULTS

5.1 Patient Population

Between September 1, 2000 and February 28, 2001 at The Ottawa Hospital and October 1, 2000 to March 31, 2001 at the Kingston General Hospital, 380 patient visits were screened for enrollment in the study and 208 patients were actually enrolled (see Figure 1).

5.1.1 Excluded Patients

43.0% of excluded patients were in atrial fibrillation for greater than 48 hours or could not tell when their current episode of atrial fibrillation had begun. 40.1% had been previously enrolled in the study. 15.1% were in an unstable clinical condition requiring immediate electrical cardioversion, and a further 1.7% were allergic to one of the drugs that may have been used. No patients were excluded because they were under 18 years of age or because they were pregnant.

The comparison between the included and excluded groups are shown in Table 2. The excluded group were older than those included. The mean heart rate and respiratory rate were statistically significantly different between the two groups but the differences were not clinically important. The average mean arterial pressure was not significantly different between those included and excluded.

Figure 1. Flow diagram of patients' progress through the study.

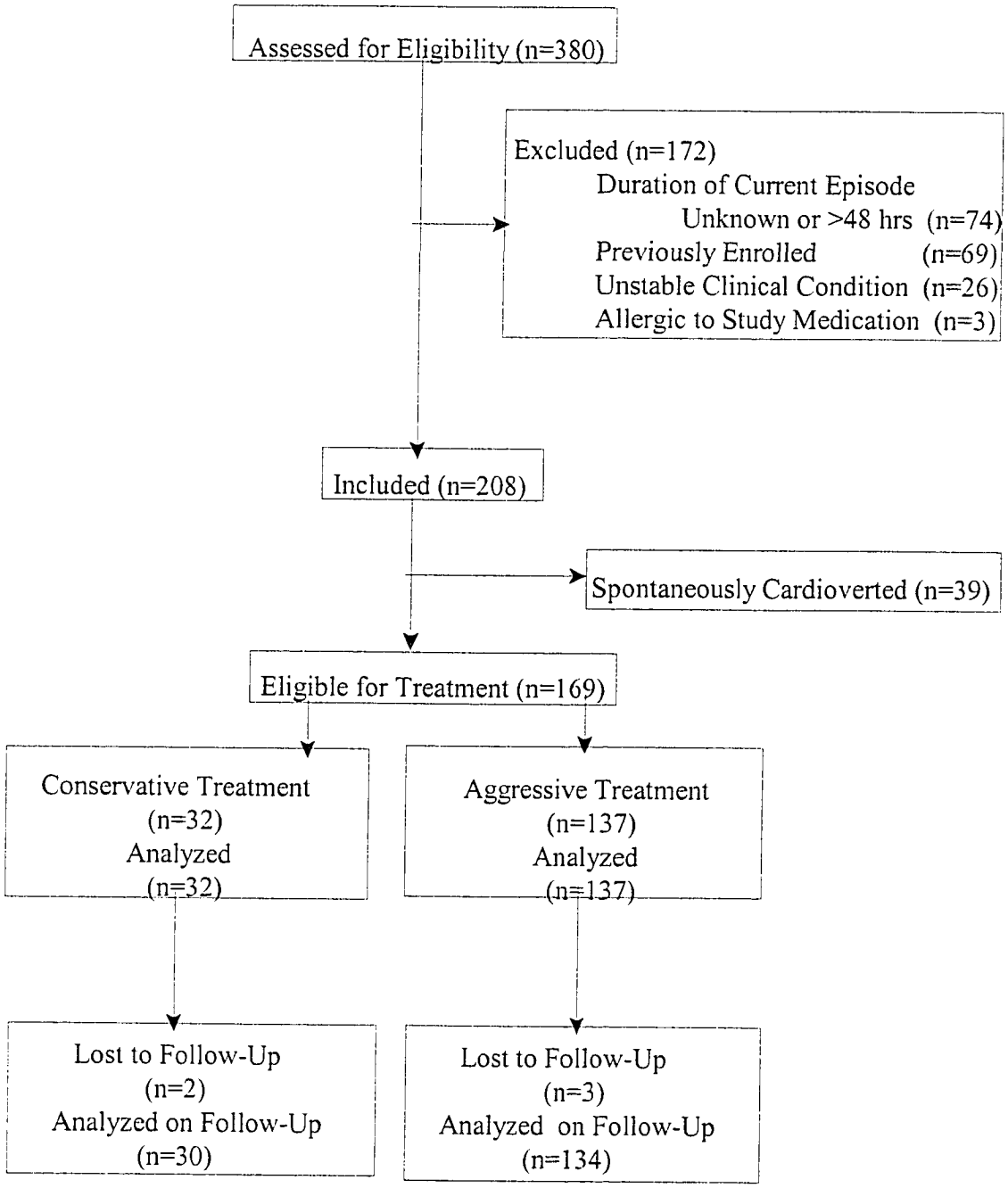


Table 2. Characteristics of Included and Excluded patients. Values are means (standard deviation).

	Overall n=380	Included n=208	Excluded n=172	p value
Age, yrs	67.5 (14.5)	64.4 (14.8)	71.1 (13.2)	<0.001
Heart Rate, bpm	118.4 (33.0)	121.6 (32.8)	114.6 (33.0)	0.04
Respiratory Rate, bpm	19.9 (5.1)	18.9 (4.2)	21.1 (5.8)	<0.001
Mean Arterial Pressure, mm Hg	102.0 (19.1)	102.9 (20.0)	100.8 (17.9)	0.28

5.1.2 Spontaneous Conversion

Of the 208 patients, 39 spontaneously converted to sinus rhythm within 30 minutes of their presentation to the emergency department without receiving any treatment. As indicated earlier, it was felt that this group converted too early to say that the treating physician was following a particular treatment approach. This group was not further analyzed.

5.2 Baseline Characteristics

Thirty-two patients were treated in a conservative manner only. Of the 137 who were treated in an aggressive manner, pharmacologic cardioversion alone was attempted in 80, pharmacologic then electrical cardioversion was attempted in 47, and electrical cardioversion alone was attempted in 10.

Table 3 lists the demographic characteristics for the study patients. The patients treated conservatively were significantly older (mean age 70.3 years, standard deviation 11.0) than those treated aggressively (mean age 61.9 years, s.d. 15.0). Other characteristics such as sex, heart rate, mean blood pressure, and respiratory rate were not significantly different between the two groups. The majority of patients were seen at the Civic Campus of the Ottawa Hospital. The patients at the Civic Campus were also more likely to be treated aggressively (89.1%) than those at the General Campus (69.4%) or the Kingston General Hospital (73.1%) (p=0.01).

This was the first episode of atrial fibrillation for 60 patients (35.5%). These patients presented to the emergency department sooner than those with recurrent atrial fibrillation. They also had a slightly higher heart rate, but this was not statistically significant (Table 4). These first-onset atrial fibrillation patients were not treated differently than those with recurrent atrial fibrillation (p=0.76).

Ninety-six (92.3%) of those who had experienced atrial fibrillation in the past had been successfully treated for this condition previously. Thirty-three (34.4%) had converted with rate control only, 46 (47.9%) were cardioverted by pharmacologic means, and 39 (40.6%) were electrically cardioverted (percentages add up to more than 100 as all methods that were successful in the past were recorded) (see Table 5). Those with a past history of converting with rate control medications were more likely to be treated conservatively

Table 3. Baseline characteristics of study patients. Values are means (standard deviation) except where indicated.

	Overall n=169	Conservative n=32	Aggressive n=137	p value
Mean Age, years	63.5 (14.7)	70.3 (11.0)	61.9 (15.0)	0.001
Age Range, years	25-93	43-91	25-93	--
Male, n (%)	103 (60.9%)	19 (59.4%)	84 (61.3%)	0.84
Mean Heart Rate, bpm	120.8 (32.2)	115.3 (28.4)	122.1 (33.0)	0.25
Heart Rate Range, bpm	50-202	68-163	50-202	--
Mean Arterial Blood Pressure, mm Hg	102.4 (20.1)	106.9 (29.4)	101.3 (17.0)	0.31
Respiratory Rate, bpm	18.8 (4.0)	20.3 (5.1)	18.4 (3.6)	0.09
Past History of Atrial Fibrillation, n (%)	109 (64.5%)	20 (62.5%)	89 (65.4%)	0.76
Other Past Medical History, n (%)	132 (78.1%)	24 (77.4%)	108 (80.6%)	0.75
Hospital Attended, n (%) - Civic	92 (54.4%)	10 (31.3%)	82 (59.9%)	0.01
- General	36 (21.3%)	11 (34.4%)	25 (18.2%)	
- Kingston	41 (24.3%)	11 (34.4%)	30 (21.9%)	
Mean Duration of Current Episode, hours	8.8 (10.4)	8.7 (12.5)	8.8 (9.9)	0.97
Median Duration of Current Episode, hours (Interquartile Range)	4 (2, 12)	3.5 (1.5, 9.8)	5.0 (2.1, 12.0)	0.22

Table 4. Baseline characteristics of patients with first-onset and recurrent atrial fibrillation. Values are means (standard deviation) except where indicated.

	First Onset n=60	Recurrent n=109	p value
Mean Age, years	64.2 (16.3)	63.3 (13.8)	0.69
Male, n (%)	31 (52.5%)	71 (65.1%)	0.11
Mean Heart Rate, bpm	127.3 (30.1)	117.5 (33.0)	0.06
Mean Arterial Blood Pressure, mm Hg	100.4 (18.3)	103.2 (20.9)	0.4
Mean Respiratory Rate, bpm	19.1 (4.0)	18.7 (4.0)	0.55
Hospital Attended, n (%) - Civic	28 (47.5%)	64 (58.7%)	0.27
- General	16 (27.1%)	19 (17.4%)	
- Kingston	15 (25.4%)	26 (23.9%)	
Mean Duration of Current Episode, hours	6.6 (7.7)	10.0 (11.5)	0.02
Median Duration of Current Episode, hours (IQR)	3 (2, 8)	5 (2.1, 13)	0.05

during the index visit. Those who were electrically cardioverted in the past were more likely to be treated aggressively.

One hundred and thirty-two patients (78.1%) had other medical conditions recorded on their chart. Medical conditions were only noted where they were specifically recorded on the chart. The most common condition was hypertension, recorded for 54 patients

Table 5. Detailed past history of atrial fibrillation. The positive cases are expressed as a percentage of the valid cases. The total percentages of the three different treatment methods add up to more than 100 because all previously successful methods were noted (i.e. patients could have more than one successful method).

	Overall		Conservative		Aggressive		
	Valid cases, n	No. Pos, (%)	Valid cases, n	No. Pos, (%)	Valid cases, n	No. Pos, (%)	p value
Past History of Atrial Fibrillation	168	109 (64.9)	32	20 (62.5)	136	89 (65.4)	0.76
Previously Successfully Treated	104	96 (92.3)	19	18 (94.7)	85	78 (91.8)	0.66
Method Previously Successful							
Rate Control	96	33	18	10 (55.6)	78	23 (29.5)	0
Pharmacologic	96	46 (47.9)	18	9 (50.0)	78	27 (47.4)	0.84
Electrical	96	39 (40.6)	18	3 (16.7)	78	36 (46.2)	0

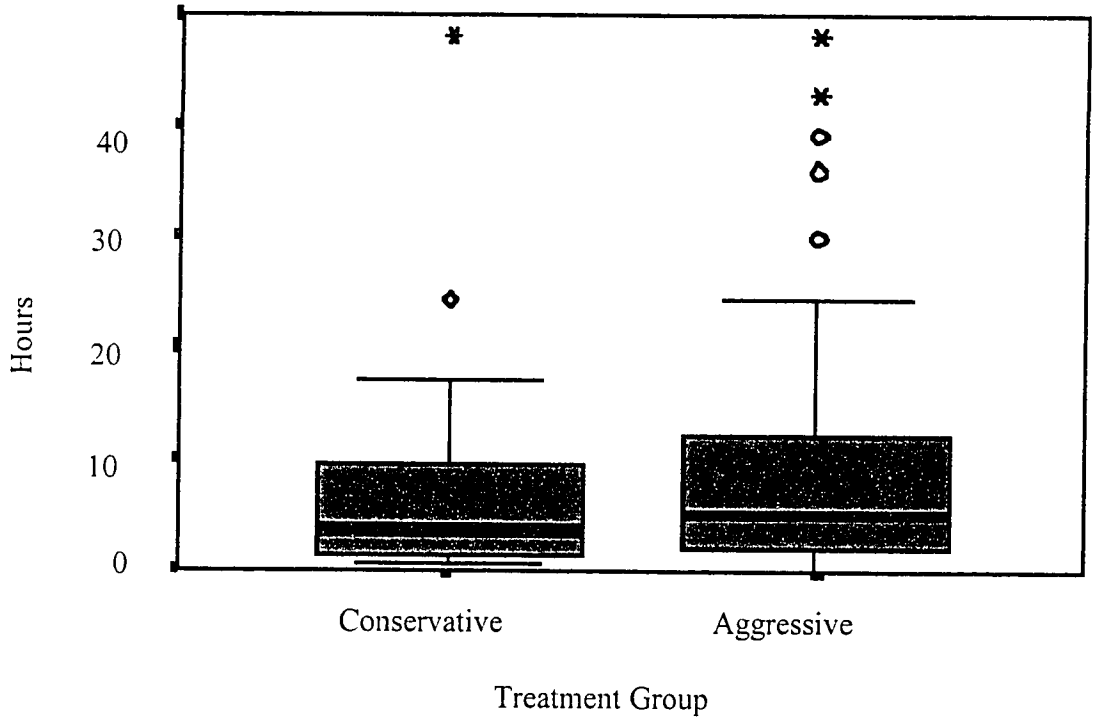
(60.7%)(see Table 6). Other conditions, in descending order of occurrence were ischemic heart disease (52.1%), valvular heart disease (43.2%), congestive heart failure (31.7%), thyroid disease (28.9%), diabetes mellitus (23.2%), past cerebrovascular accident (22.5%), and past thromboembolic disease (11.8%). Other conditions were recorded in 97 patients and included elevated cholesterol (25 patients), cancer (9), asthma/COPD (8), palpitations or tachycardias (6), sleep apnea (4), and abdominal aortic aneurysm (3). Coronary artery disease was the only condition that was found more commonly in one group.

Table 6. Detailed other past medical history. The positive cases are expressed as a percentage of the valid cases (those that had information about the condition).

	Overall		Conservative		Aggressive		p value
	Valid Cases, n	No. Pos, (%)	Valid Cases, n	No. Pos, (%)	Valid Cases, n	No. Pos, (%)	
Hypertension	89	54 (60.7)	19	11 (57.9)	70	43 (61.4)	0.78
Coronary Artery Disease	73	38 (52.1)	19	15 (78.9)	54	23 (42.6)	<0.01
Valvular Heart Disease	44	19 (43.2)	12	3 (25.0)	32	16 (50.0)	0.13
Diabetes Mellitus	56	13 (23.2)	16	4 (25.0)	40	9 (22.5)	0.84
Thyroid Disease	45	13 (28.9)	13	4 (30.8)	32	9 (28.1)	0.86
Congestive Heart Failure	41	13 (31.7)	12	6 (50.0)	29	7 (24.1)	0.15
Cerebrovascular Accident	40	9 (22.5)	11	2 (18.2)	29	7 (24.1)	0.69
Thromboembolism	34	4 (11.8)	9	1 (11.1)	25	3 (12.0)	0.94
Other	105	97 (92.4)	18	16 (88.9)	87	81 (93.1)	0.62

The duration of the current episode of atrial fibrillation was short for many patients. The median duration of atrial fibrillation was four hours (interquartile range 2-12 hours); 132 (78.1%) presented within 12 hours and 158 (93.5%) presented within 24 hours of onset. (See Figure 2).

Figure 2. Boxplot of duration of current episode of atrial fibrillation prior to presentation to the emergency department. Thick horizontal line represents median; Upper and lower limits of boxes represent 75th and 25th percentiles; Vertical lines extend to a maximum of 1.5 times the height of the box; Circles represent outliers and asterisks represent extremes (cases more than 3 times the box height away from the top of the box).



5.3 Emergency Department Treatment

The details of the patients' course in the emergency department are listed in Table 7. More of the patients in the conservative group were given medication to control their heart rate (62.5% vs 44.5%), although this was not statistically significant ($p = 0.07$).

Table 7. Course of treatment in emergency department. Values are number (percent) except where indicated.

	Overall n=169	Conservative n=32	Aggressive n=137	p value
Received Rate Control Medication	81 (47.9)	20 (62.5)	61 (44.5)	0.07
Successful Conversion to Sinus Rhythm	126 (74.6)	11 (34.4)	115 (83.9)	<0.001
Post-Cardioversion ECG Abnormal	21 (12.4%)	4 (12.5%)	17 (12.4%)	0.99
Cardiac Enzymes Abnormal	1 (0.6)	0 (0)	1 (0.7)	0.11
Admitted	23 (13.6)	12 (37.5)	11 (8.0)	<0.001
Consultations in the Emergency Department	76 (45.0)	14 (43.8)	62 (45.3)	0.88
Outpatient Consultation Advised	121 (71.6)	20 (62.5)	101 (73.7)	0.21
Median Length of Stay in Emergency Department (IQR), hours	5.3 (3.8, 7.8)	5.9 (3.6, 10.6)	5.3 (3.8, 7.4)	0.26
Median Physician-to-Disposition Time (IQR), hours	4.2 (2.8, 7.0)	5.1 (3.2, 8.5)	4.5 (3.2, 7.0)	0.22

5.3.1 Successful Cardioversion

Slightly more than one-third (34.4%) of the conservatively treated group spontaneously converted to sinus rhythm. Significantly more patients (83.9%) in the aggressively treated

group converted to a sinus rhythm ($p<0.001$). Fifty-one percent of 127 patients were successfully cardioverted with pharmacologic agents and 87.7% of 57 patients were successfully electrically cardioverted.

5.3.2 Post-Cardioversion Tests

There was no difference between the treatment groups in the proportion of patients who had abnormal electrocardiograms after conversion to sinus rhythm. Twenty-one patients had an abnormality noted on their post-conversion ECG and this did not differ between the groups. It may be more appropriate to consider these abnormal ECG's as a percentage of just those who converted to sinus rhythm. Using those who converted as the denominator, post-conversion ECG's were abnormal in 36.4% of the 11 who spontaneously converted and 15.0% of the 113 who were successfully treated aggressively ($p = 0.09$).

Only one patient had an abnormal cardiac enzyme test. This patient, an 88 year-old man, presented with 5 hours of symptoms. He received 500 mg of IV procainamide then was converted with 100 J of electricity on the first attempt. His CK and Troponin T levels were elevated but he was not admitted. His post-conversion ECG showed a normal sinus rhythm with premature atrial complexes but no signs of ischemia or injury.

5.3.3 Hospital Admission

Significantly more patients in the conservative treatment group were admitted to hospital

(37.5% vs 8.0%, p<0.001). Predictably, hospital admission was also strongly correlated with spontaneous conversion or successful cardioversion to sinus rhythm; 37.8% of patients who did not convert were admitted and 4.8% of those who converted (p<0.001).

5.3.4 Consultations

Other specialists were consulted in under half of the cases and this did not differ between groups. Most commonly, cardiologists were consulted, in 12 (37.5%) conservatively treated patients and 33 (24.1%) aggressively treated patients (p=0.13). Anesthetists were consulted on 32 occasions, all for those patients who were treated aggressively (see Table 8).

Table 8. Details of emergency department consultations.

	Overall n=169	Conservative n=32	Aggressive n=137	p value
Anesthesia, n (%)	32 (18.9)	0 (0)	32 (23.4)	<0.001
Cardiology, n (%)	45 (26.6)	12 (37.5)	33 (24.1)	0.13
Internal Medicine, n (%)	2 (1.2)	2 (6.25)	0 (0)	0.17
Other, n (%)	1 (0.6)	0 (0)	1 (0.7)	0.63

Outpatient consultations were recommended in 71.6% of cases, and this did not differ between the two groups. Patients were advised equally often to follow-up with a cardiologist or with their family physician. There was a trend for aggressively treated

patients to be referred more often to a cardiologist and conservatively treated patients to their family physician, but this was not statistically significant (see Table 9).

Table 9. Details of Outpatient Consultations.

	Overall n=169	Conservative n=32	Aggressive n=137	p value
Cardiology, n (%)	68 (40.2)	8 (25.0)	60 (43.8)	0.11
Family Physician, n (%)	63 (37.3)	14 (43.8)	49 (35.8)	0.08
Other, n (%)	18 (10.7)	5 (15.6)	13 (9.5)	0.18

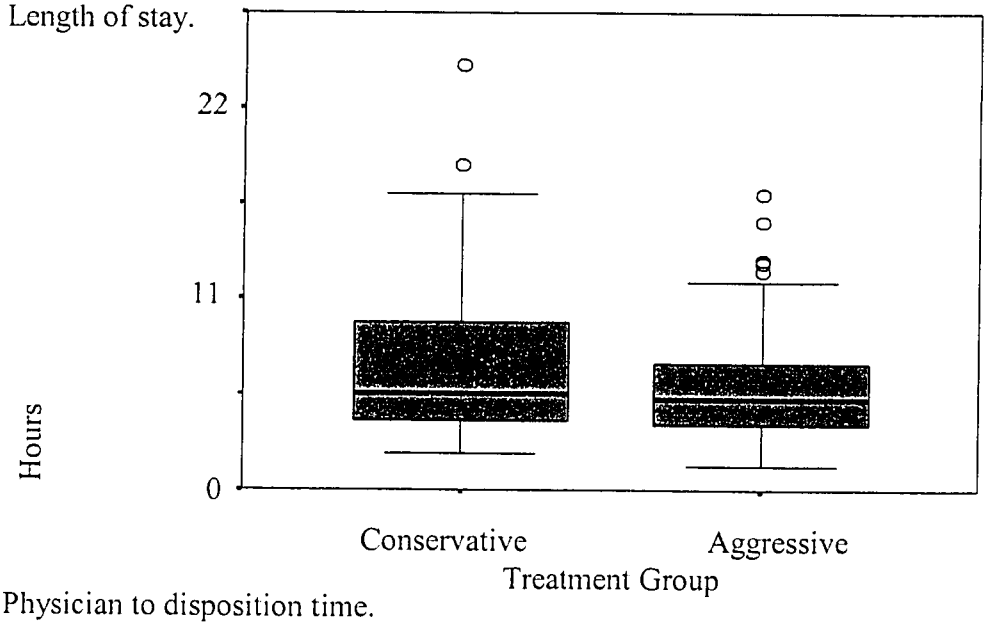
5.3.5 Length of Time in Emergency Department

Figure 3 and Table 7 show the amount of time that patients spent in the emergency department, from the time they presented to the triage desk to the time of disposition ("length of stay"), and the time from being seen by the emergency physician to the time of disposition ("physician-to-disposition time").

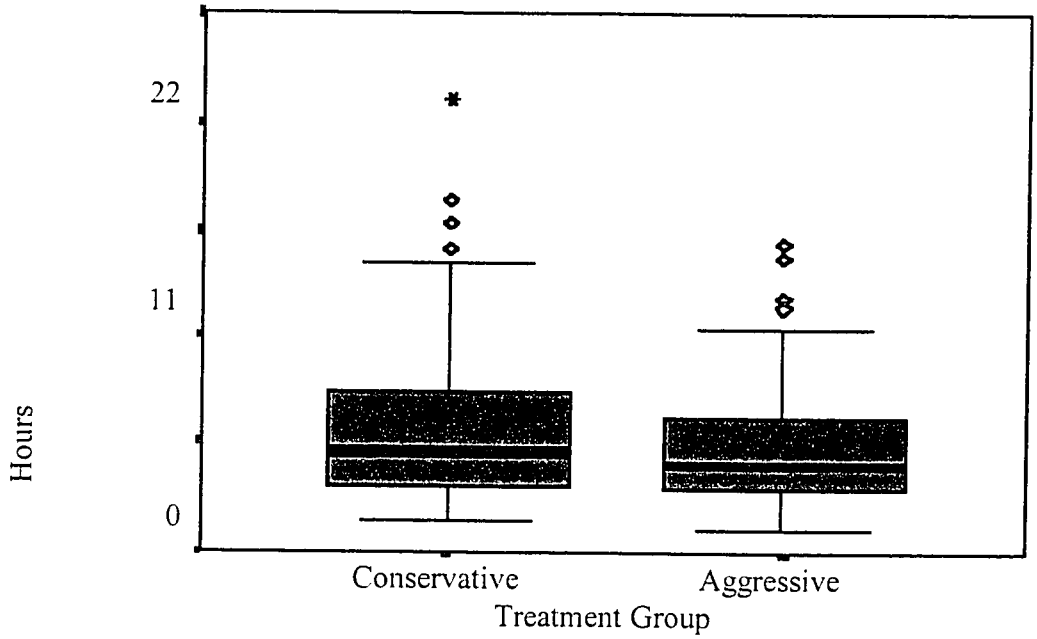
The median (interquartile range) length of stay was 5 hours, 18 minutes (3:47, 7:45); 5:37 (3:55, 10:36) for the conservatively treated group and 5:16 (3:46, 7:22) for the aggressively treated group (p=0.26). The median (interquartile range) physician-to-disposition time was 4:09 (2:45, 6:57); 5:06 (3:10, 8:27) for the conservative group and 4:30 (3:10, 7:00) for the aggressively-treated group (p=0.22).

Figure 3. (a) Boxplot of patients' length of stay in emergency department; (b) boxplot of time from emergency physician seeing patient to patient disposition. Thick horizontal line represents median; Upper and lower limits of boxes represent 75th and 25th percentiles; Vertical lines extend to a maximum of 1.5 times the height of the box; Circles represent outliers and asterisks represent extremes (cases more than 3 times the box height away from the top of the box).

(a) Length of stay.



(b) Physician to disposition time.



5.4 Follow-Up Interview

Four weeks after their emergency department visit, the patients were interviewed over the telephone. One hundred and sixty-four of the patients were contacted (97.0%). Two patients in the conservative treatment group could not be contacted, as was the case with three in the aggressive treatment group. Results are summarized in Table 10.

5.4.1 Follow-up Care

One hundred and thirty-four patients were given a follow-up appointment or made one themselves and 95.5% of them, 128, kept the appointment (Table 10). During that appointment, fifteen patients had further investigations ordered; eight patients had an echocardiogram arranged, six had Holter monitoring arranged, two a stress test, and one each an angiogram and pulmonary function tests. Ten patients had further therapy arranged or done; four had further cardioversion arranged, four were booked for ablation, and one each were booked for pacer programming and angioplasty. There were no differences between the treatment groups regarding further investigation or treatment. Fifty-six were given a prescription, significantly more of the conservatively treated group than the aggressively treated group ($p=0.01$). The prescriptions included new or increased doses of beta-blockers (16), warfarin (12), amiodarone (6), sotalol (6), digoxin (4), other antiarrhythmic agents (4), anti-platelet agents (5), diuretics (4), and ACE Inhibitors (2).

Table 10. Results of four-week follow-up interview. Values are number (percent).

	Overall n=164	Conservative n = 30	Aggressive n = 134	p value
Follow-up Appointment	128 (78.0)	24 (80.0)	104 (77.6)	0.48
Outpatient Investigation Ordered	15 (9.1)	1 (3.3)	14 (10.4)	0.31
Elective Treatment Arranged	10 (6.1)	3 (10.0)	7 (5.2)	0.39
Given Prescription at Follow-up	56 (34.1)	16 (53.3)	40 (29.9)	0
Recurrence of Atrial Fibrillation by four week interview	56 (34.1)	10 (33.3)	46 (34.3)	0.92
MD Visit for Recurrence of Atrial Fibrillation	33 (20.1)	7 (23.3)	26 (19.4)	0.63
Received Treatment for Recurrence	21 (12.8)	5 (16.7)	16 (11.9)	0.63
MD Visit for Any Reason	57 (34.8)	10 (33.3)	47 (35.1)	0.86
Symptoms	60 (36.6)	14 (46.7)	46 (34.3)	0.21
Willingness to Enrol in Future Randomized Controlled Trial	112 (68.3)	16 (53.3)	96 (71.6)	0.1

5.4.2 Recurrence of Atrial Fibrillation

About one-third of the patients in the conservative and aggressive groups were in atrial fibrillation at the time of the four-week interview (33.3% vs 34.3%, respectively). Two of the conservatively treated patients who converted in the emergency department had a recurrence, compared to 42 of the aggressively treated group who had converted in the emergency department (see Table 11). An alternative way to consider this is that 30.0% of

Table 11. Patients who reported being in atrial fibrillation at the four-week interview, according to whether they were successfully converted to sinus rhythm in the emergency department.

(a) Conservative treatment group.

		Converted in the Emergency Department		
		Yes	No	Totals
In Atrial Fibrillation at Four-Week Follow-up	Yes	2	8	10
	No	9	11	20
Totals		11	19	30

(b) Aggressive treatment group.

		Converted in the Emergency Department		
		Yes	No	Totals
In Atrial Fibrillation at Four-Week Follow-up	Yes	42	4	46
	No	69	17	86
Totals		111	21	132

conservatively treated patients were in sinus rhythm both in the emergency department and at the four-week follow-up, compared to 52.3% of the aggressively treated patients ($p=0.03$).

The majority of patients with a recurrence, 7 in the conservative group and 26 in the aggressive group, sought medical attention for this recurrence (Table 10). Twenty-seven

visited an emergency department, twelve saw a cardiologist, eight saw their family physician, and one each saw an internist, an endocrinologist, and a cruise ship doctor. None visited a walk-in clinic. Seventeen were treated during this visit: three received rate control medication only, five were pharmacologically cardioverted, and nine were electrically cardioverted. Thirteen received a prescription, but only three were for new medications, one for warfarin and sotalol, one for warfarin alone, and one for a beta-blocker to be used on an as-needed basis.

Slightly over one-third of the patients visited a physician for any reason; 10 (33.3%) in the conservative and 47 (35.1%) in the aggressive groups. One of the physician visits in the conservative group was for weakness, which may be a symptom related to atrial fibrillation; however, this patient did not note a recurrence of their atrial fibrillation but noted lightheadedness on the follow-up interview. One of the physician visits in the aggressive group was for a TIA; this patient also did not note any recurrence of atrial fibrillation and did not note any symptoms on the follow-up interview.

5.4.3 Symptoms

Slightly more patients in the conservative group (46.7%) reported having symptoms than those in the aggressive group (34.3%) but this difference was not statistically significant (Table 10). Similarly, there were no significant differences for any individual symptom (Table 12).

Table 12. Details of symptoms on follow-up interview. Values are number (percent).

	Overall n=164	Conservative n=30	Aggressive n=134	p value
Palpitations	38 (23.2)	7 (23.3)	31 (23.1)	0.98
Fatigue	29 (17.7)	7 (23.3)	22 (16.4)	0.38
Dyspnea	22 (13.4)	6 (20.0)	16 (11.9)	0.24
Chest Pain	16 (9.8)	3 (10.0)	13 (9.7)	0.96
Lightheadedness	15 (9.1)	4 (13.3)	11 (8.2)	0.48
Loss of Consciousness	0 (0)	0 (0)	0 (0)	N/A*
Cerebrovascular Accident	0 (0)	0 (0)	0 (0)	N/A

*N/A: Not Applicable

5.4.4 Quality of Life

The patients who were treated aggressively had a higher physical component summary (PCS) score on the SF-36 than those treated conservatively (Table 13). They also scored higher on the Physical Functioning and Role-Physical component scales, which both contribute highly to the PCS score, and Vitality, which contributes less to the PCS. The difference in scores for Bodily Pain and General Health did not reach statistical significance, nor did the scores for Social Functioning, Role – Emotional, or Mental Health. There was not a significant difference in the scores on the mental component summary (MCS) score.

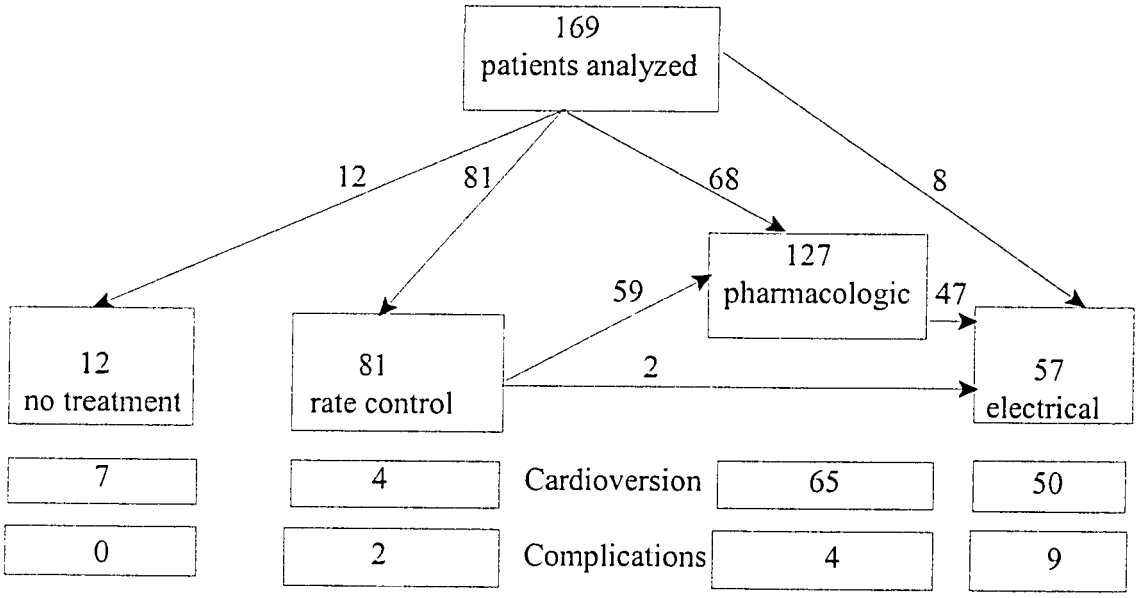
Table 13. Quality-of-life at four-week follow-up interview. All values are mean (standard deviation).

SF - 36 Scale	Overall n=164	Conservative n=30	Aggressive n=134	p value
Physical Component Summary	46.0 (11.9)	41.2 (11.9)	47.1 (12.1)	0.01
Mental Component Summary	51.3 (10.5)	48.4 (12.9)	51.1 (10.0)	0.38
Physical Functioning	74.7 (28.8)	59.8 (33.1)	77.6 (27.5)	0.01
Role - Physical	60.5 (44.7)	44.8 (44.0)	64.5 (44.8)	0.02
Bodily Pain	80.2 (27.2)	74.4 (26.8)	82.0 (27.2)	0.1
General Health	68.3 (19.5)	61.9 (20.8)	67.8 (19.8)	0.15
Vitality	56.0 (26.5)	44.8 (30.2)	58.1 (25.1)	0.03
Social Functioning	82.9 (25.4)	75.4 (33.7)	84.2 (23.8)	0.31
Role - Emotional	76.7 (38.9)	63.2 (44.8)	76.1 (39.3)	0.1
Mental Health	78.6 (15.9)	73.5 (19.4)	78.6 (15.5)	0.25

5.5 Individual Treatment Methods

The two treatment groups, conservative and aggressive, which comprise the primary analysis of this study encompass three separate treatments of atrial fibrillation: rate control, pharmacologic cardioversion, and electrical cardioversion. In the present study, there were several combinations of these three treatments used by the treating physicians and examining each of these individually provides useful information that cannot be appropriately analyzed under the conservative / aggressive dichotomy (Figure 4).

Figure 4. Details of treatment methods used for patients. The top box indicates the total number of patients analyzed in the study. The next row indicates the number of patients who received each treatment, as labelled. The row of boxes labelled "cardioversion" indicate the number of patients who converted to sinus rhythm during the treatment indicated in the box above. The row of boxes labelled "complications"indicate the number of patients who had complications during the treatment indicated above.



5.5.1 Successful Conversion to Sinus Rhythm

There were eight possible combinations of the three treatment methods, and all eight were used by treating physicians in this study (Table 14). Electrical cardioversion by itself and in combination with rate control had the highest conversion rates (100%). The lowest rate of conversion was in those who received rate control medication only (20.0%). The no treatment group had spontaneous conversion in 58.3%

Table 14. Outcomes of individual treatment methods. Values are numbers (percent).

Treatment Method		Number of Cases	Success
No Treatment		12	7 (58.3)
Rate Control	Only	20	4 (20.0)
Pharmacologic	Only	42	37 (88.1)
	With Rate Control	38	28 (73.7)
Electrical	Only	8	8 (100)
	with Rate Control	2	2 (100)
	with Pharmacologic	26	25 (96.2)
	All Three	21	15 (71.4)

5.5.1.1 Rate Control

Twenty patients received only rate control agents, of whom four (20.0%) converted. The most common medications used were beta-blocking agents (41 patients), diltiazem (29), verapamil (10), digoxin (5), and adenosine (3).

5.5.1.2 Pharmacologic Cardioversion

One hundred and twenty-seven patients received pharmacologic cardioversion agents, which were successful in 65 (51.2%) of the cases. There was no difference in the success of pharmacologic cardioversion whether the patients received rate control (47.5%) or not (54.4%) (p=0.43).

One hundred and four patients received procainamide, 14 received amiodarone, six received both, and one each received oral sotalol and oral propafenone. Focussing only on those who received just amiodarone or procainamide, the proportion who were successfully cardioverted with procainamide was higher (51.9% vs 21.4%, p = 0.03). Of the six patients who received both procainamide and amiodarone, four successfully cardioverted; one of the other two also failed electrical cardioversion and the last did not go on to attempt electrical cardioversion. The patient who received propafenone successfully converted and the patient who received sotalol did not convert (electrical cardioversion was not attempted and the patient was discharged still in atrial fibrillation).

5.5.1.3 Electrical Cardioversion

Fifty-seven patients had electrical cardioversion attempted; it was successful in 50 (87.7%). Two patients had rate control and electrical cardioversion, and 21 received all of rate control and pharmacologic agents and electrical cardioversion. Because of the small size of the one group it was decided to analyze all those who received rate control and compare them to all those who did not. This showed that fewer of the 23 patients who received rate control (73.9%) were successfully cardioverted electrically than the 34 who did not (97.1%) ($p<0.01$).

5.5.1.3.1 Electrical Cardioversion Following Pharmacologic Attempt

Forty-seven of the patients who were not cardioverted pharmacologically proceeded to receive electrical cardioversion. Forty (85.1%) of these patients were successfully

cardioverted, 89.2% of the 37 who had received procainamide and 77.8% of the nine of those who received amiodarone. The one patient who received both procainamide and amiodarone was not successfully cardioverted. The proportion who were successfully cardioverted did not differ for those who received procainamide or amiodarone ($p = 0.34$).

5.5.1.3.2 Primary Electrical Cardioversion

Only eight patients had primary electrical cardioversion and all eight were successfully cardioverted.

5.5.1.3.3 Energy Used

Various amounts of energy were used for the electrical cardioversion, generally following a pattern of increasing energy for subsequent shocks. Table 15 shows the outcomes of these patients according to the amount of energy used on the initial attempt. Generally, the higher the initial dose used, the higher the proportion successful on the first attempt and the proportion eventually successful, with the exception of the 200 J group, and the fewer shocks needed.

5.5.2 Complications Due to Treatment

Complications were recorded according to the individual treatment method received rather than according to combination of treatment (Table 16).

Table 15: Outcomes of electrical cardioversion attempt according to initial dose of energy used. Number of Shocks indicates the mean number of shocks required to produce cardioversion in cases where it was successful (Subsequent shocks were usually of a higher dose than the one preceding). Values are numbers except where indicated.

Initial Dose of Energy (J)	Cases	Success on First Attempt, %	Eventual Success, %	Number of Shocks
50	6	16.7	83.3	3
100	34	50	94.1	1.6
200	14	42.9	71.4	1.4
300	3	100	100	1

Table 16. Complications of individual treatment methods. Values are numbers (percent).

Treatment Method		Number of Cases	Complications
No Treatment		12	0 (0)
Rate Control		81	2 (2.5)
Pharmacologic	No Rate Control	68	2 (5.4)
	With Rate Control	59	2 (7.1)
Electrical	Only	8	1 (12.5)
	Rate Only	2	1 (50.0)
	Pharm Only	26	3 (11.5)
	Both	21	4 (19.0)

5.5.2.1 No Treatment

By definition, there were no complications attributable to treatment in this group.

5.5.2.2 Complications of Rate Control

Of the 81 patients who received rate control medication, two (2.5%, 95% Confidence Interval 0.7% to 8.7%) had complications. One patient became hypotensive and one developed first-degree atrioventricular block. Both patients were successfully cardioverted electrically and neither were admitted to hospital.

5.5.2.3 Complications of Pharmacologic Cardioversion

Of the 127 who received pharmacologic cardioversion agents, four (3.1%, 95% CI: 1.2 - 7.8%) had complications. One patient had hypotension, bradycardia, and chest pain. One patient each had hypotension, first-degree atrioventricular block, and chest pain. The patient with hypotension had the infusion of procainamide stopped and was admitted to hospital. The other three patients were successfully cardioverted pharmacologically and were discharged from the emergency department.

5.5.2.4 Complications of Electrical Cardioversion

Of the 57 who received electrical cardioversion attempts, 9 (15.8%, 95% CI: 8.5 - 27.4%) had complications - two related to sedation and seven directly due to the electrical cardioversion attempt. Of the two patients who had complications from the sedation, one suffered hypoxia, electrical cardioversion was unsuccessful and the patient was admitted.

The other patient became apneic, had shallow respirations when an oropharyngeal airway was inserted, and was successfully electrically cardioverted and discharged. Each patient had received both rate control and pharmacologic cardioversion agents prior to electrical. Both patients received propofol and fentanyl as sedation agents.

Two of the seven patients with complications of electrical cardioversion had also received both rate control (metoprolol) and pharmacologic cardioversion agents (procainamide and amiodarone). One had a burn on his chest and the other had a rash on his chest. Neither was successfully cardioverted. Neither was admitted. Three patients had received pharmacologic agents only (procainamide in two and amiodarone in the other). One had bradycardia, one an atrioventricular block, and one hypotension. All were successfully cardioverted and discharged from the emergency department. One patient had received IV metoprolol as a rate control agent and propofol for sedation, as well as atropine. After successful cardioversion he had bradycardia, but was not admitted. There was one complication in the group that underwent primary electrical cardioversion. The patient was sedated with propofol and atropine and suffered hypotension and bradycardia after successful cardioversion. He was not admitted.

In summary, there were 15 complications. In four of these cases, cardioversion was unsuccessful and two of these patients were admitted.

5.6 Willingness to Enrol in Randomized Controlled Trial

At the end of the follow-up interview, patients were asked whether they would be willing to participate in a randomized controlled trial comparing treatments for atrial fibrillation. One hundred and twelve of the patients were willing to participate in such a trial (68.3%). This was higher for those treated aggressively (71.6%) than those treated conservatively (53.3%), but this was not statistically significant (p=0.06).

6 DISCUSSION

6.1 Summary of Findings

6.1.1 Conservative Treatment Approach

Slightly more than one-third (34.4%) of conservatively treated patients converted to sinus rhythm in the emergency department and 37.5% were admitted to hospital. There were no cases where cardiac markers of injury were positive. There were very few complications related to conservative treatment and none that led to admission. At the follow-up interview, one-third of patients reported visiting a physician in the four weeks after the emergency department visit. One-third reported a recurrence of atrial fibrillation; 30% were in sinus rhythm at emergency department discharge and at the four-week follow-up interview.

6.1.2 Aggressive Treatment Approach

83.9% of aggressively treated patients converted to sinus rhythm in the emergency department and only 8.0% were admitted to hospital. One case had elevated markers of cardiac injury (0.7%) and that patient was not admitted. There were few complications related to aggressive treatment, 3.1% associated with pharmacological treatment and 15.8% associated with electrical cardioversion. One patient in each of the pharmacological (0.8%) and electrical (1.8%) groups was admitted. At the follow-up interview, one-third of patients reported visiting a physician in the four weeks after the emergency department visit. Slightly more than one-third (34.3%) reported a recurrence

of atrial fibrillation; 52.3% were in sinus rhythm at emergency department discharge and at the four-week follow-up interview.

6.2 Interpretation

6.2.1 Objective 1

a) To prospectively estimate the efficacy of conservative (rate control) treatment of paroxysmal atrial fibrillation.

34.4% of patients were in sinus rhythm at the time of emergency department discharge. 37.5% of the conservatively treated patients were admitted to the hospital. 30% of patients were in sinus rhythm at emergency department discharge and at the four-week follow-up interview.

Compared to the previous study at the Ottawa Civic Hospital, the present study had a higher rate of conversion with conservative management, although Michael et al did not examine those who received no treatment.[12]

b) To prospectively estimate the efficacy of aggressive (pharmacologic or electrical cardioversion) treatment of paroxysmal atrial fibrillation.

83.9% of patients were in sinus rhythm at the time of emergency department discharge. 8.0% of the aggressively treated patients were admitted to the hospital. 52.3% of patients were in sinus rhythm at emergency department discharge and at the four-week follow-up

interview. The proportions successfully cardioverted with pharmacologic and electrical cardioversion were similar between the two studies.

6.2.2 Objective 2

a) To prospectively estimate the proportion of patients treated conservatively who experience immediate or short-term (within four weeks) complications related to emergency department treatment of paroxysmal atrial fibrillation.

There were no complications, by definition, in the group which received no treatment. 2.5% of those treated with rate control agents suffered complications, none of which led to hospital admission.

b) To prospectively estimate the proportion of patients treated aggressively who experience immediate or short-term (within four weeks) complications related to emergency department treatment of paroxysmal atrial fibrillation.

Attempts at pharmacologic cardioversion had complications in 3.1% of patients and electrical cardioversion had complications in 15.8%. Very few of these complications led to admission: 0.8% of pharmacologic cardioversion attempts and 1.8% of electrical cardioversion attempts.

There were more complications in the group electrically cardioverted than were expected, mostly hypotension and/or bradycardia. Only one complication in this group led to admission, so the episodes of hypotension and/or bradycardia were likely transient. The

definitions of bradycardia and hypotension in the present study did not include a time factor and may have been too sensitive. The majority of complications in this group occurred in patients who had received rate control and/or pharmacologic cardioversion agents. These drugs may have played a role in causing these complications.

There were more complications than were found in the chart review by Michael et al (3%, 9%, and 0%, respectively). The present study had a similar proportion of complications for rate control, lower for pharmacologic conversion but much higher with electrical cardioversion. The proportion admitted was higher in the present study. The chart review excluded some patients with additional cardiac complications who would have been included in the present study; these patients could have been at higher risk for complications. As well, while both studies used similar definitions of complications, there were some complications in the current study that may not have been considered as such by Michael et al; for example a rash on the chest was a complication in the current study. The present study and the chart review had similarly low proportions of complications that led to admission.

However, the total proportion admitted was higher in the present study. Some of the differences may be accounted for by the fact that Michael et al's study was a retrospective chart review while the present study was prospective. As well, the present study involved the General Campus and Kingston General Hospital emergency departments, which treated more patients conservatively than did the Civic Campus and where more patients

were admitted. The result of the present study may be more representative of the general population of paroxysmal atrial fibrillation patients who are treated in various hospitals.

A large majority of patients had enzyme tests ordered to detect myocardial damage or infarction. Almost none of these patients had a positive test, and none of those with a positive test were admitted. This low proportion of myocardial damage, and the lack of effect of the results on patient management, suggests that the tests are not of value and may be safely omitted from the treatment of atrial fibrillation patients. Abnormalities on the electrocardiogram also did not affect management but the electrocardiogram does serve another purpose, that of confirming the conversion of the patient's rhythm back to a sinus rhythm.

The present study had no episodes of thromboembolism at four-week follow-up, and just one patient who reported a TIA. This is consistent with Weigner et al's finding of 0.8% clinical thromboembolic events.[28] Three patients in the aggressive treatment group were lost to follow-up; if all three of them had thromboembolic events (the worst-case scenario), the 95% confidence interval around the result of 2.2% events (0.7% - 6.2%) would still be consistent with Weigner et al (95% confidence interval 0.2% - 2.4%). Thirty-three of the patients in the present study were taking warfarin, which probably lowered the incidence of thromboembolic events. In Weigner's study, patients on warfarin with a therapeutic INR were excluded.

6.2.3 Objective 3

To determine the enrollment rate and follow-up rate that would be expected in a randomized controlled trial comparing different treatments for paroxysmal atrial fibrillation.

Over six months at three sites, 380 patients were screened and 169 were eligible and enrolled in the present study. One-third of patients contacted at four-week follow-up stated that they would not be willing to participate in a trial comparing treatments for paroxysmal atrial fibrillation. The explanation of the trial was brief (see Appendix B) and more patients may be willing to participate after receiving more complete information. Follow-up was very high (97.0%) at four weeks. Patients were willing to participate in the follow-up interview and the SF-36. Patients were not requested to return to the hospital for reassessment in the present study, which they would be required to do in a randomized controlled trial. This may lower the proportion of patients willing to participate.

6.2.4 Objective 4

To determine the ease of use and comprehensiveness of data collection procedures used for the patient's emergency department visit and follow-up interview.

As expected, the data collection procedure used resulted in little missing data. The most frequently missed items on the medical record were the patient's respiratory rate and individual items of the past medical history. However, information was available on all patients who presented to the emergency department (with some missing data) whereas

the alternative, requiring physicians to complete a data form, would have likely resulted in fewer forms being filled out, as is the case in concurrent studies.

Review of patient charts was not difficult at any site. Each site kept a log of all patients who presented to the emergency department and each site had a copy of the medical chart on site in the emergency department. Old medical records were easily retrieved when required.

There was a very low number of patients who were lost to follow-up; the majority of charts had alternative contact people and phone numbers listed which were used when required. Patients were generally willing to answer all of the questions in the structured follow-up interview, including the SF-36.

6.2.5 Objective 5

To provide a descriptive profile of the patients presenting to the emergency department with paroxysmal atrial fibrillation.

This study quantifies the burden of acute paroxysmal atrial fibrillation. Over six months, 128 patients were enrolled at The Ottawa Hospital, whose total emergency department visits the year previously totalled 111, 445. After including those patients in acute paroxysmal atrial fibrillation who were excluded because they spontaneously converted (39 patients) or who had been previously enrolled in this study (69 patients), and doubling

this data which covered six months, paroxysmal atrial fibrillation of less than 48 hours duration constituted 0.4% of all emergency department visits.

6.2.5.1 Baseline Characteristics

There was a wide range of ages but the population was mostly elderly. The majority of the patients were male and had a past history of atrial fibrillation, as well as other medical conditions. Their vital signs upon presentation to the emergency department showed mild tachycardia but their blood pressures and respiratory rates were in the normal range (only a small percentage of the population that was screened were excluded because of unstable blood pressures). Patients were more likely to be treated the same way, conservatively or aggressively, as they had been treated successfully in the past. Those who were older and those who had a history of coronary artery disease were more likely to be treated conservatively.

The two treatment groups were similar except that the conservatively treated group was older and a higher proportion had a past history of coronary artery disease. This may show a reluctance to aggressively treat those who were older (although the age range was wider in the aggressive treatment group), even though there is no evidence that age, per se, is associated with more complications from treatment. Analogous to the situation in the present study, there are other cardiovascular conditions such as myocardial infarction where the elderly are less likely to receive aggressive therapy, despite increased benefit.[54] Similar to the situation with the elderly, there may be a reluctance to treat those who had

coronary heart disease, although other conditions that could be expected to create concern in physicians, such as congestive heart failure, past cerebrovascular accident, and thromboembolism, were not differentially distributed between the two treatment groups.

The patient's past history of receiving successful treatment of atrial fibrillation was related to treatment group. Those who were successfully treated in the past with conservative or aggressive therapy were more likely to be treated the same way in the current visit. This may reflect patient choice or indicate a pattern of practice at that site. Not all treatment methods that were tried previously with the patient were recorded, only those that were successful. It may be possible that other treatments were tried in a particular patient but were not successful; physicians and patients would probably be less likely to use or accept these unsuccessful methods again.

Those with new-onset atrial fibrillation were similar in their other characteristics to those with recurrent atrial fibrillation, except that those with new-onset presented to the emergency department earlier in their episode. Patients with no experience with atrial fibrillation may have been more concerned about the symptoms than those who had experienced them before, and therefore presented sooner.

The vast majority of patients presented within 24 hours of onset of atrial fibrillation. This may indicate that symptoms were bothersome enough to cause patients to present to the emergency department soon after the fibrillation began.

6.2.6 Objective 6

To describe the clinical course of paroxysmal atrial fibrillation patients.

6.2.6.1 Emergency Department

Few were admitted to the hospital from the emergency department. The majority were discharged home whether they converted to sinus rhythm or not. None were admitted for myocardial damage or abnormalities on the post-cardioversion electrocardiogram.

6.2.6.2 Follow-up

Our finding of one-third recurrence or persistence of atrial fibrillation at four weeks is higher than that of Suttorp et al who recorded approximately 22% recurrence at the same time.[55] They found that the recurrence rate was much higher during the first 8 weeks of follow-up than during later follow-up; the present study was not designed to calculate an incidence rate or survival analysis for recurrence. There was no difference between those with new-onset and previous history of atrial fibrillation in proportions with recurrence at four weeks.

The present study did not collect information regarding any prescriptions which were given upon discharge from the emergency department. Prophylactic anti-arrhythmic medications may decrease the recurrence rate.

6.2.7 Objective 7

To determine patients' quality of life.

The aggressively treated patients' mental and physical component summary scores on the SF-36 were similar to the US population norms (50.0). For the conservatively treated patients, the physical component summary score was lower than for the US population, while the mental component summary score was similar.

6.2.8 Exploratory Comparisons

Exploratory comparisons were performed on the conservative and aggressive treatment groups. These are only meant to be hypothesis-generating as there are potential biases which may invalidate such comparisons. Since the study did not involve randomization, there may have been a selection bias when physicians decided on which treatment approach to use for a particular patient. For example, the baseline characteristics (Table 3) show that mean age was significantly different between the groups.

The proportion of patients admitted was lower in the aggressive treatment group, while the length of stay in the emergency department was not significantly different between the two groups. This suggests that there was a lower use of resources in the aggressive treatment group, as the decreased proportion of patients admitted to hospital was not offset by increased time in the emergency department (which is used here as a proxy for

resource use in the emergency department), nor by increased physician visits in the four weeks following the emergency visit.

Similar proportions of patients in both treatment groups had follow-up appointments and, at the time of the appointment, had further investigation or treatment. Furthermore, similar proportions of the two groups had unscheduled physician visits for recurrence and physician visits for any other reason. The study did not show, up to the four-week point after the emergency visit, a difference in medical visits between patients in the conservative and aggressive treatment groups. This finding, combined with the trend of slightly more conservatively treated patients experiencing symptoms, suggests that there was not a difference in the severity of the symptoms or in the demands on the medical system between the groups. However, this cannot be said with certainty, since the data collection procedure did not inquire into the number of physician visits, just whether any had occurred.

The quality of life four weeks after the emergency visit, as scored on the SF-36, was higher on the physical summary score for those treated aggressively and there was not a significant difference on the mental summary score. Using quality of life score as a proxy for utility and patient preference, this suggests a patient preference for aggressive treatment. However, baseline quality of life scores were not done at the time of the emergency visit, so changes in quality of life could not be calculated and it cannot be

assumed that the conservatively treated and aggressively treated groups had similar scores at the time of the emergency visit.

The higher quality of life in aggressively-treated patients in the present study suggests that there is benefit in attempting to cardiovert patients when they present in the emergency department, even though there was not a difference in symptoms. There is still no good evidence from a randomized controlled trial, however, on whether converting patients from atrial fibrillation to sinus rhythm is better for patients than simply trying to prevent symptoms.[56] This has not been studied in paroxysmal atrial fibrillation but Hohnloser et al found an improved quality of life but not a difference in symptoms when patients with chronic atrial fibrillation population were cardioverted.[19] Studies are ongoing to look at the benefit of continuing prevention of atrial fibrillation, such as the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM), but this study is looking at patients with longer duration of atrial fibrillation than in the present study.[57]

6.2.9 Evolving Pattern of Practice

In the face of conflicting or non-existent evidence, other factors have a large influence on practice patterns. These other factors include physician or patient choice, whether for reason of convenience, past practice or experience, and expert opinion.[58, 59] In the case of clinically stable paroxysmal atrial fibrillation, the presence of this situation is reflected in the variety of recommendations issued in the various guidelines, as well as the variety of practice recorded in the present study.

Practice patterns were in evolution at the participating sites even as the present study was being planned. Cardiologists at the General site had approached the emergency department regarding a proposed protocol for aggressive treatment of paroxysmal atrial fibrillation (AA Cwinn, personal communication). This protocol was not in place at the time of the study but more patients were treated aggressively than was expected based on the physicians' stated practice style. This had the effect of decreasing the number of patients who were treated conservatively. This shift of practice from expected was also noted at the Kingston General Hospital. The large difference in numbers between the treatment groups weakens the ability of the study to observe differences in outcomes for the given overall study size..

6.2.10 Relevance of Findings to Clinical Practice

Recognizing the limits of the present study, it suggests that aggressive treatment is related to higher conversion to sinus rhythm, that this persists to the four-week point, and that aggressive treatment is related to a higher quality of life at the four-week point. This supports the assumed logic behind the evolving pattern of practice noted above: that being in sinus rhythm is better for patients.

More people are discharged home in sinus rhythm after aggressive treatment than conservative treatment. The patients in sinus rhythm are, presumably, able to return to their normal level of activity upon emergency department discharge.

This study also supports the concept that aggressive treatment of paroxysmal atrial fibrillation of less than 48 hours duration is safe, with few complications immediately and in the short-term.

From the point of view of the healthcare system, there is a decreased proportion of hospital admission in the aggressively-treated patients. This lower resource utilization is not offset by more unscheduled physician visits in the follow-up period.

These findings, while they are not definitive, may be expected to hasten the further evolution of practice to more aggressive therapy.

6.3 Strengths

This was the first prospective study of paroxysmal atrial fibrillation treated in the emergency department. Previous studies were chart reviews, usually without comparison groups. The present study had little chance of misclassification bias since medical records were required, for medicolegal reasons, to record drugs given and electrical cardioversion attempted, and this information determined the classification. As well, this information was recorded by nursing staff as well as physicians, which further reduced the chance that aggressive treatment was not recorded.

The population in this study was relatively consistent, compared to other studies. Inclusion and exclusion criteria were set to ensure that only those with paroxysmal atrial fibrillation were included, and only those whose current episode of atrial fibrillation lasted less than 48 hours. Other studies have included patients with other supraventricular tachycardias, including atrial flutter, as well as those with chronic atrial fibrillation. The heterogeneity of patients in other studies makes it difficult to compare results; for example the proportion of patients with spontaneous conversion ranges from 0 to 68% in various studies.[33, 36] The 34.4% proportion who spontaneously cardioverted in the conservative treatment group is in the midrange of these findings.

Because physician-completed forms were not used, data was available on all patients identified from review of the patient logs. There was minimal loss to follow-up and all patients contacted agreed to participate in the follow-up interview. This resulted in a minimal possibility of a biased estimate of outcomes.

This is the first study to follow patients after their emergency department visit and, thus, the first to provide information on short-term outcomes including recurrence of atrial fibrillation and unscheduled physician visits.

The study is the first to formally evaluate quality of life in patients with acute paroxysmal atrial fibrillation.

6.4 Limitations

This study was a prospective observational cohort study, not a randomized controlled trial. There is evidence that the results of non-randomized trials can be different from randomized trials and that, on average, there is an increased effect size in the non-randomized studies, although this is not universal.[60] In the present study, there may have been an increased estimate of effect size due to selection bias. Physicians may have been reluctant to aggressively treat those who were sicker and those who were sicker may have had a decreased probability of successful cardioversion. In fact, the groups were significantly different in age and history of coronary heart disease; as these are both factors which can reasonably be expected to influence treatment approach and success, the difference may indicate selection bias. Because of the limitations of the dataset, especially the small sample size, it would not be possible to entirely account for these differences. A randomized trial theoretically would control for unknown factors as well as the known factors.

The large difference in size of the treatment groups decreased the power of the study to detect differences between those treated conservatively and those treated aggressively.

Data was not collected at the time of the subject's emergency visit, except for the subjects who presented to the Kingston General Hospital during hours when a research nurse was on duty. This was unavoidable as no similar infrastructure was in place at either campus of the Ottawa Hospital and funding was inadequate to hire a nurse to be available to

interview patients at the time of the emergency visit. As expected, there were only a few cases where desired information was not recorded on the medical record, mostly details of the patient's past medical history.

Also as a result of the study methodology, it was not possible to obtain baseline information on quality of life and calculate changes after the emergency department visit. It is possible that those treated aggressively had higher quality of life prior to any treatment being given.

Because follow-up was only performed on one occasion four weeks after the emergency department visit, there was no way to determine what the actual time in sinus rhythm was for the patients. Survival analysis would require sequential follow-up on a regular and frequent basis. Ideally, this would also include electrocardiographic confirmation of the rhythm. This lack of early follow-up also affected the ability to detect very short-term symptoms and assess short-term changes in quality of life.

As well, follow-up sooner after the emergency department visit may have shown more difference in symptoms and quality of life, as the main benefit would be expected shortly after treatment and this may decrease as recurrence occurs with time.

The vast majority of patients presented within 24 hours of onset of atrial fibrillation. Generally, the shorter the duration of atrial fibrillation, the more effective the attempts at

cardioversion, although this relationship has not been proven for durations under 48 hours. If this relationship is also true in the first 48 hours of paroxysmal atrial fibrillation, then the findings of the present study may not be generalizable to the population who present between 24 and 48 hours after onset of atrial fibrillation.

6.5 Future Research

Although the present study was not designed to provide definitive data, it does suggest that aggressive treatment has a higher success rate in converting people to a sinus rhythm and that this persists to the four-week point with a corresponding higher quality of life. Because of the above-mentioned limitations and potential biases in the present study, these findings need to be confirmed with a randomized controlled trial comparing conservative and aggressive treatment. The design of this trial will be based on the results of the present study, as planned when the present study was itself designed. Such a trial is outlined here.

6.5.1 Objectives

1) The primary objective will be to compare the success of aggressive and conservative treatment of paroxysmal atrial fibrillation of less than 48 hours duration. Success will be defined as the proportion of subjects who are converted to sinus rhythm in the emergency department and who continue in sinus rhythm for two weeks.

2) To compare the proportions of patients who were cardioverted and stay in sinus rhythm for eight weeks. The eight week time is used based on Suttorp et al's study showing that the recurrence rate of atrial fibrillation is highest in the first eight weeks.[55]

3) To compare the spontaneous cardioversion rates in those who have not converted in the emergency department.

4) To compare the incidence rates of first recurrence of atrial fibrillation in those who have been converted in the emergency department.

5) To compare subjects' course in the emergency department.

6) To compare the proportions who have symptoms in the follow-up period and their change in quality of life from baseline recorded in the emergency department.

7) To compare those with new-onset atrial fibrillation and those with recurrent paroxysmal atrial fibrillation as to whether they have different success rates.

8) To compare those who present in the first 24 hours of their paroxysm and those who present 24 - 48 hours after onset as to whether they have different success rates.

6.5.2 Study Population

The definition of atrial fibrillation used in the present study seems appropriate and using onset of symptoms to determine the time of onset of the episode seems appropriate and safe and is supported by the literature. Thus, the same inclusion and exclusion criteria as used in the present study will be used in the trial.

6.5.2.1 Subgroups

There was no suggestion in the present study that those with new-onset or recurrent paroxysmal atrial fibrillation had different outcomes. Therefore, both populations will be included in the trial. Subgroup analysis will be performed to determine if the outcomes are different in the two groups.

Very few of the patients in the present study presented after more than 24 hours of fibrillation. Since it is not yet known whether this population is more resistant to attempts at cardioversion than those presenting within 24 hours, subgroup analysis will be done based on duration of presenting episode. The cutoff will be those presenting up to 24 hours and those presenting with more than 24 hours of fibrillation.

Since stratification at the time of randomization will be done on the basis of centre, it would not be practical to have three stratification factors (centre, new-onset or recurrent, and less than or greater than 24 hours) which would lead to many strata. Subgroup

analysis of the data will have nearly equal power as stratified randomization if the sample size is over 100.[61]

6.5.3 Patient Screening and Enrollment

The screening of the patient for inclusion and exclusion criteria will be done in the emergency department. Funding will determine whether physicians will be requested to perform this task or whether dedicated research personnel will be hired to do so. Ideally, minimizing the burden on an already overworked medical staff will minimize the number of patients who are inappropriately not screened for the study.

Once screened, patients will be approached regarding the trial and be asked for informed consent. The present study indicates that approximately one-third of patients will decline to participate, although this may change once the study is explained to them.

Once enrolled, patients will be considered trial subjects and will have baseline information collected. This information includes age, sex, vital signs, information regarding past history of atrial fibrillation, treatments used previously and results, current medications, past medical history. The SF-36 quality of life instrument will be administered at this time as a baseline measure.

Randomization will be performed using a random numbers table, in a blocked randomization pattern with random block size varying from 4 to 8. Randomization will be

stratified by participating centre. Appropriate measures will be taken to conceal the allocation of the next subject, such as opaque sealed envelopes or using a protected computer program to randomize subjects.

6.5.4 Outcome Measures

Objective 1: Proportion converted to sinus rhythm in the emergency department, proportion in sinus rhythm at two weeks.

Objective 2: Proportion in sinus rhythm at eight weeks.

Objective 3: Proportion in sinus rhythm at 24 and 48 hours.

Objective 4: Time to first recurrence of atrial fibrillation (for those who converted in the emergency department).

Objective 5: Proportion who suffer complication in the emergency department, length of stay in the emergency department, emergency department consultations, proportion admitted to the hospital, proportion with abnormalities on lab tests for myocardial damage.

Objective 6: Presence of symptoms at reassessment visits, change in SF-36 score between reassessment visits and emergency department baseline, unscheduled physician visits, further treatment(s) for atrial fibrillation, presence of thromboembolism. Specific symptoms, based on the current study, will be palpitations, fatigue, dyspnea, chest pain, lightheadedness.

6.5.5 Experimental Treatment and Follow-up

A standardized treatment plan would be designed for both groups. This would be designed in conjunction with participating centres. Consultations and admission to hospital would be left to the discretion of the treating physician. Reasons for consultations and admissions will be recorded.

Follow-up will be repeated. On a regular basis, subjects will be requested to return for a follow-up appointment which would include an electrocardiogram and assessment of symptoms. This should extend at least to the eight week period for the secondary objective (1). As well, there should be more frequent telephone follow-up in the first week after the emergency department visit for the primary objective. This follow-up will require considerable resources and may have to be altered due to funding constraints and to reduce the burden on the subjects. For example, the weekly follow-up may be done over the telephone with only certain situations requiring in-person assessment.

6.5.6 Blinding

It would not be reasonable to blind the subject or the treating team to the treatment allocation. Measurement bias in the assessment of outcomes will be minimized by blinding the assessor at follow-up to treatment allocation and requesting the subject not to inform the assessor. This, of course, would require that the assessor not be the same person who enrolled the subject; this has funding implications as more staff will need to be hired.

6.5.7 Statistical Analysis

Analysis will be done on an intention-to-treat basis. Data will initially be described using proportions for dichotomous outcomes and mean, and standard deviation for continuous outcomes. Comparisons will be performed using chi-squared for dichotomous outcomes and Student's t-test for continuous outcomes. Survival analysis will be performed for time to recurrence. The probability of type I error will be set at 0.05.

6.5.8 Sample Size

The formula for sample size calculation for a trial with two equally sized groups and with a dichotomous outcome is

$$2N = 4\,(Z_\alpha + Z_\beta)^2\;\; p_{av}\,(1 - p_{av}) \,/\, (p_c - p_i)^2$$

where Z_α is the value of Z that corresponds to the chance of type I error (1.96 for a two-sided probability of 0.05), Z_β is the value of Z that corresponds to the chance of type II error (0.84 for a probability of 0.2), and p_{av} is the arithmetic mean of the occurrence rates in the control (p_c) and intervention (p_i) groups.[61] In this formula, it is expected that the intervention will reduce the occurrence rate of the (unwanted) outcome, treatment failure.

Using the primary outcome as described above, the data to calculate the sample size would come from the results of the present study. The proportion of conservatively treated subjects (the "control group") who were in sinus rhythm at emergency department discharge and stayed in sinus rhythm up to the four-week follow-up (30.0%) is the best

estimate we have. Based on this the occurrence rate of the outcome in the control group (p_c) is estimated to be 0.700.

The minimum clinically important difference will be decided after consultation with other investigators and emergency physicians. See table 17 for the sample size required to have 80% power to detect various absolute risk reductions, using the rates of occurrence provided from the present study and a 0.05 chance of type I error. For example, the randomized trial would require 357 subjects in each arm of the trial to have 80% power to detect an absolute risk reduction of 10%. Assuming that 45% of screened patients would be eligible and that one-third of patients would decline to participate (from the present study) and a 10% loss to follow-up, 2643 patients would need to be screened.

This would require a 42 month enrollment period using the same three sites and assuming the same rate of patient presentation to the emergency department; other sites have already expressed interest in participating in such a randomized trial, which would decrease the time required to enrol the required sample size and increase the generalizability of the results. The sample size calculation assumes a 10% loss to follow-up. This is higher than the 3% loss to follow-up found in the present study because the burden on subjects is higher in the trial than in the present study, and it is expected that this higher burden will be associated with a lower participation level.

Table 17. Sample size required for 80% power to detect given absolute risk reductions. The formula for sample size is given in the text. The chance of Type I error is set at 0.05 (two-tailed) and the occurrence rate in the control group is 70%. The formula to calculate number of patients to screen from number of subjects needed in each arm is given in the text.

Occurrence Rate in Intervention Group	Absolute Risk Reduction	Number of Subjects Required in Each Arm of the Study	Total Number of Patients Required to be Screened
0.69	0.01	33, 238	246, 205
0.67	0.03	3, 760	27, 847
0.65	0.05	1, 376	10, 192
0.6	0.1	357	2, 643
0.55	0.15	164	1, 210
0.4	0.2	95	697

6.5.9 Alternative Trial

When combined with the evolution of practice noted earlier, the results of the present study may suggest to some that the randomized trial described above would not have the necessary clinical equipoise or uncertainty required to justify such a trial. It is also possible that this trial may fail (not enrol adequate numbers of subjects) because physicians at the participating centres may not be willing to enrol their patients in a trial comparing conservative and aggressive treatments.[62] However, a trial comparing primary electrical cardioversion and initial pharmacologic cardioversion may be of interest.

Alternatively, a three-arm study (conservative treatment, initial pharmacologic, and primary electrical cardioversion) may interest some physicians because their patients would have a two-thirds chance of being allocated to an aggressive treatment arm (one could also adjust the proportions allocated to conservative or aggressive treatment). These alternatives or variations of the randomized trial described above would have less power to detect a difference between conservative and aggressive treatment, for a given total sample size. They would only be considered if it appears that the original trial is not feasible due to lack of participation of centres or physicians.

6.6 Conclusions

This was the first prospective study, to our knowledge, examining emergency department treatment of paroxysmal atrial fibrillation of up to 48 hours duration. Aggressive treatment was associated with 83.9% conversion to sinus rhythm in the emergency department, 8.0% hospital admission, and 52.3% of patients being in sinus rhythm both at emergency department discharge and at four-week follow-up. Conservative treatment was associated with 34.4% conversion in the emergency department, 37.5% hospital admission and 30.0% of patients being in sinus rhythm both at emergency department discharge and at four-week follow-up. There was a low incidence of complications and a very low incidence of complications requiring admission. At four-week follow-up, approximately one-third of all patients reported symptoms. Quality of life scores were similar to the US population norms for the aggressively treated group. The physical

component summary score was similar to the population norm, although the mental component summary score was lower. No major complications were recorded at the four-week follow-up interview, and one-third reported physician visits for any reason.

The results of the present study provide data which will allow planning of a randomized controlled trial comparing treatment methods for paroxysmal atrial fibrillation, with a goal of finding the safest and most effective treatment for this condition.

REFERENCES

1. Levy S. Pharmacologic management of atrial fibrillation: current therapeutic strategies. Am Heart J 2001;141:

2. Takahashi N, Seki A, Imataka K, Fujii J. Clinical features of paroxysmal atrial fibrillation. An observation of 94 patients. Jpn Heart J 1981;22:143-9.

3. Asplund K, Beermann B, Bergfeldt L, Blomstrom P, Lundqvist CB, Boman K. Treatment of atrial fibrillation. Eur Heart J 1993; 14:1427-33.

4. Waktare J, Camm J. Atrial Fibrillation. London: Martin Dunitz Ltd; 2000.

5. Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. J Am Coll Cardiol 2000;36:1303-9.

6. Shapiro EP, Effron MB, Lima S, Ouyang P, Siu CO, Bush D. Transient atrial dysfunction after conversion of chronic atrial fibrillation to sinus rhythm. Am J Cardiol 1988;62:1202-7.

7.Petersen P, Godtfredsen J. Embolic complications in paroxysmal atrial fibrillation. Stroke 1986; 17:622-6.

8. Connors S, Dorian P: Management of supraventricular tachycardia in the emergency department. Can J Cardiol 1997;13(Suppl A):19A-24A.

9. Li H, Easley A, Barrington W, Windle J: Evaluation and management of atrial fibrillation in the emergency department. Emerg Med Clin North Am 1998;16:389-403.

10. Ostrander LD Jr, Brandt RL, Kjelsberg MO, Epstein FH. Electrocardiographic findings among the adult population of a total natural community, Tecumseh, Michigan. Circulation 1965;31:888-98.

11. Feinberg WM, Blackshear JL, Laupacis A, et al: Prevalence, age distribution, and gender of patients with atrial fibrillation: Analysis and implications. Arch Intern Med. 1995;155:469-473.

12. Michael JA, Stiell IG, Agarwal S, Mandavia DP. Cardioversion of paroxysmal atrial fibrillation in the emergency department. Ann Emerg Med 1999; 33:379-387.

13. Chan BTB, Schull MJ, Schultz SE. Atlas Report: Emergency department services in Ontario, 1993-2000. Toronto: Institute for Clinical Evaluative Sciences; 2001 .

14. Upshaw CB. Hemodynamic changes after cardioversion of chronic atrial fibrillation. Arch Int Med 1997; 157:1070-6.

15. Jung F, DiMarco JP: Treatment Strategies for Atrial Fibrillation. Am J Med 1998; 104:272-286.

16. Anonymous. Advanced Cardiovascular Life Support: Section 5: Pharmacology I: Agents for Arrhythmias. Circulation 2000; 102 [Suppl I]: I-112 - I-128.

17. Ware JE. the SF-36 health survey manual and interpretation guide. Boston (MA): The Health Institute, New England Medical Center; 1993.

18.Jung W, Herwig S, Newman D, Akhtar M, Wood K, Ayers G, et al. Impact of atrial fibrillation on quality of life: a prospective, multicenter study [abstract]. J Am Coll Cardiol 1999; 33:104A

19. Hohnloser SH, Kuck KH, Lilienthal J for the PIAF Investigators. Rhythm or rate control in atrial fibrillation -- pharmacological intervention in AF (PIAF): a randomised trial. Lancet 2000; 356:1789-94.

20. Bubien RS, Knotts-Dolson SM, Plumb VJ, Kay N. Effect of radiofrequency catheter ablation on health-related quality of life and activities of daily living in patients with recurrent arrhythmias. Circulation 1996;94: 1585-91.

21.Rubart M, Zipes DP. Genesis of Cardiac Arrhythmias: Electrophysiological Considerations. In: Braunwald E, Zipes DP, Libby P, editors. Heart Disease: A Textbook of Cardiovascular Medicine. 6th ed. Philadelphia (PA): W. B. Saunders Co; 2001. p. 659-99.

22. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. Circulation 1995;92:1954-68.

23. Zipes DP. Electrophysiological remodeling of the heart owing to rate. Circulation 1997;95:1745-8.

24. Hobbs WJC, Fynn S, Todd DM, Wolfson P, Galloway M, Garratt CJ. Reversal of atrial electrical remodeling after cardioversion of persistent atrial fibrillation in humans. Circulation 2000;101:1145-51.

25.Albers GW, Dalen JE, Laupacis A, Manning WJ, Petersen P, Singer DE. Antithrombotic therapy in atrial fibrillation. Chest 2001;119: 194S-206S.

26. Manning WJ, Weintraub RM, Waksmonski CA, Haering Jm, Rooney PS, Maslow AD, et al. Accuracy of transesophageal echocardiography for identifying left atrial

thrombi. Ann Intern Med 1995;123:817-22.

27. Stoddard MF. Dawkins PR. Prince CR. Ammash NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. J Am Coll Cardiol 1995; 25:452-9.

28.Weigner MJ, Caulfield TA, Danias PG, Silverman DI, Manning WJ. Risk for clinical thromboembolism associated with conversion to sinus rhythm in patients with atrial fibrillation lasting less than 48 hours. Ann Intern Med 1999; 126:615-20.

29. Pelosi F Jr, Morady F. Evaluation and management of atrial fibrillation. Med Clin North Am 2001; 85:225-44.

30.Page RL, Wilkinson WE, Clair WK, McCarthy EA, Pritchett ELC. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. circulation 1994; 89:224-7.

31.Bhandari AK, Anderson JL, Gilbert EM, Alpert BL, Henthorn RW, Waldo AL et al. Correlation of symptoms with occurrence of paroxysmal supraventricular tachycardia or atrial fibrillation: A transtelephonic monitoring study. Am Heart J 1992; 124:381-6.

32. The Planning and Steering Committees of the AFFIRM study for the NHLBI AFFIRM investigators. Atrial fibrillation follow-up investigation of rhythm management -- the AFFIRM study design. Am J Cardiol 1997; 79:1198-202.

33. Danias PG, Caulfield TA, Weigner MJ, Silverman DI, Manning WJ. Likelihood of spontaneous conversion of AF to SR. J Am Coll Cardiol 1998;31: 588-92.

34. Bellandi F, Simonetti I, Leoncini M, Frascarelli F, Giovannini T, Maioli M, et al. Longterm efficacy and safety of propafenone and sotalol for the maintenance of Sinus rhythm after conversion of recurrent symptomatic atrial fibrillation. Am J Cardiol 2001;88:640-5.

35. Talajic M, MacDonald RG, Nattel S. Restoration of sinus rhythm in patients with atrial fibrillation. Can J Cardiol 1996; 12(Suppl A):29A-35A.

36. Golzari H, Cebul RD, Bahler RC. Atrial fibrillation: Restoration and maintenance of sinus rhythm and indications for anticoagulation therapy. Ann Intern Med 1996; 125:311-23.

37. Alpert MA. Medical cardioversion of atrial fibrillation. Chest 2000; 117:1529-31.

38. Lown B, Amarasingham R, Neuman J. New method for terminating cardiac arrhythmias. JAMA 1962; 182:548-55.

39. Lown B. Electrical reversion of cardiac arrhythmias. Br Heart J 1967; 29:469-87.

40. Lown B, Perlroth MG, Kaidbey S, Abe T, Harken DE. "Cardioversion" of atrial fibrillation. New Engl J Med 1963; 269:325-31.

41. Burdick W. Carotid sinus massage and cardioversion. In: Roberts JR, Hedges JR, editors. Clinical procedures in emergency medicine. 3rd ed. Philadelphia: W.B. Saunders Co.; 1998. p. 173-185.

42. Joglar JA, Hamdan MH, Ramaswamy K, Zagrodzky JD, Sheehan CJ, Nelson LL, et al. Initial energy for elective external cardioversion of persistent atrial fibrillation. Am J Cardiol 2000;86:348-50.

43. Trohman RG, Parrillo JE. Direct current cardioversion: Indications, techniques, and recent advances. Crit Care Med 2000; 28(Suppl):N170-N173.

44. Anonymous. Advanced Cardiovascular Life Support : Section 2: Defibrillation. Circulation 2000 102 [Suppl I]: I-90 - I-94.

45. Omran H, Jung W, Rabahieh R, Ilien S, Spehl S, Wolpert C, et al. Electrical cardioversion of atrial fibrillation: is postcardioversion atrial stunning caused by electrical energy or by atrial fibrillation itself?[abstract]. J Am Coll Cardiol 1999;33:104A.

46. Oral H, Souza JJ, Michaud GF, Knight BP, Goyal R, Strickberger SA et al. Facilitating transthoracic cardioversion of atrial fibrillation with ibutilide pretreatment. N Engl J Med 1999; 340:1849-54.

47. Lesser MF. Safety and efficacy of in-office cardioversion for treatment of supraventricular arrhythmias. Am J Cardiol 1990; 66:1267-8.

48. Mulcahy B, Coates WC, Henneman PL, Lewis RJ. New-onset atrial fibrillation: When is admission medically justified? Acad Emerg Med 1996;3:114-9.

49. Nattel S. Newer developments in the management of atrial fibrillation. Am Heart J. 1995;130:1094-1106.

50. Yealy DM, Delbridge TR. Dysrhythmias. In Rosen P, Barkin R, Danzl DF, editors. Emergency Medicine: Concepts and Clinical Practice, 4ed. St.Louis:Mosby, 1998. p. 1583-630.

51. Fuster V, Ryden LR, Asinger RW, Cannom DS, Crijns HJ, Frye RL, et al. Acc/aha/esc guidelines for the management of patients with atrial fibrillation: executive summary a report of the american college of cardiology/american heart association task force on practice guidelines and the european society of cardiology committee for practice guidelines and policy conferences (committee to develop guidelines for the management of patients with atrial fibrillation) developed in collaboration with the north

american society of pacing and electrophysiology. Circulation 2001; 104:2118-50.

52. Falk RH. Atrial fibrillation. N Engl J Med 2001; 344:1067-78.

53. Jung W, Loderitz B. Quality of life in patients with atrial fibrillation. J Cardiovasc Electrophysiol 1998; 9: S177-86.

54. McLaughlin TJ, Soumerai SB, Willison DJ, Gurwitz JH, Borbas C, Guadagnoli E, et al. Adherence to national guidelines for drug treatment of suspected acute myocardial infarction: evidence for undertreatment in women and the elderly. Arch Intern Med 1996;156:799-805.

55. Suttorp MJ, Kingma JH, Koomen EM, van't Hof A, Tijssen JGP, Lie KI. Recurrence of paroxysmal atrial fibrillation or flutter after successful cardioversion in patients with normal left ventricular function. Am J Cardiol 1993; 71: 710-3.

56. Connolly SJ. Appropriate outcome measures in trials evaluating treatment of atrial fibrillation. Am Heart J 2000; 139: 752-60.

57. The planning and steering committees of the AFFIRM study for the NHLBI AFFIRM investigators. Atrial fibrillation follow-up investigation of rhythm management: the AFFIRM study design. Am J Cardiol 1997; 79: 1198-202.

58. Redelmeier DA, Ferris LE, Tu JV, Hux JE, Schull MJ. Problems for clinical judgement: introducing cognitive psychology as one more basic science. Can Med Assoc J 2001;164:358-60.

59. Croskerry P. The Cognitive Imperative: Thinking about How We Think. Acad Emerg Med 2000;7: 1223-31.

60. Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. BMJ 1998;317: 1185-90.

61. Friedman LM, Furberg CD, DeMets DL. Fundamentals of clinical trials. 3rd ed. St. Louis (MO): Mosby; 1996.

62. Sackett DL. Why randomized controlled trials fail but needn't: 1. Failure to gain "coal-face" commitment and to use the uncertainty principle. Can Med Assoc J 2000;162:1311-4.

APPENDICES

APPENDIX A. RESEARCH ETHICS BOARD APPROVAL

The Ottawa Hospital | L'Hôpital d'Ottawa

Research Ethics Board
Conseil d'éthique en recherches
761-4146 ~ 761-4902 ~ 761-5072
Fax No. ~ 761-4920

Friday, November 05, 1999

Dr. Atul Kapur
Emergency Department
Ground Floor
Ottawa Hospital - Civic Campus

Dear Dr. Kapur:

Re: Protocol # - 1999152-01H **Emergency Department Treatment of Paroxysmal Atrial Fibrillation**

Protocol approval valid until - **Saturday, November 04, 2000**

Thank you for your letter dated October 25, 1999. You have met the requirements of the Board and the above listed project has been granted approval by the Research Ethics Board. No addenda may be made in the protocol or the consent form without the Research Ethics Board review and approval.

The validation date should be indicated on the bottom of all consent forms and information sheets (see copy attached). Approximately one month prior to that time, a single renewal form should be sent to Research Services.

Medical Research Council guidelines require a greater involvement of the Research Ethics Board in studies over the course of their execution. You must maintain as part of your records copies of the signed consent form. As well, you must inform the Board of adverse events encountered during the study, here or elsewhere, or of significant new information which becomes available after the Board review, either of which may impinge on the ethics of continuing the study. The REB will review the new information to determine if the protocol should be modified, discontinued, or should continue as originally approved.

Yours sincerely,

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board

Encl.

APPENDIX B: PATIENT INFORMATION FORM

Emergency Department Treatment of Atrial Fibrillation

We are performing a study examining the treatment of atrial fibrillation, the irregular heart rate that you had when you came into the emergency department.

This study is gathering information on the treatment that you received. Please note that the treatment you received today was not affected by this study; you received the standard treatment that the emergency doctor decided was most appropriate for you. This study did not change your treatment in any way.

As part of the study, we will be telephoning you in about four weeks to ask you some questions about any other treatment you may have received and about how you are feeling.

This information will help us to develop a better picture regarding how atrial fibrillation is treated. This phone call will take about fifteen minutes.

When we call you, you are free to not answer any particular question or to end the call at any time. Your participation is entirely voluntary and will not affect your future care.

If you have any questions about this study, you may contact the principal investigator, Dr. Atul Kapur, at (613) 798-5555, extension 8688.

APPENDIX C. DATA COLLECTION FORM

Page 1 of 5 Subject Number:_____

EMERGENCY DEPARTMENT TREATMENT OF ATRIAL FIBRILLATION

DEMOGRAPHICS

Patient Initials:_____ Chart Number:_____

Age (yrs): _____ Sex: ◯Male ◯Female

Date of Visit (y/m/d):__/__/__ Hospital: ◯Civic ◯General ◯Kingston

Physician Name:_____

INITIAL VITAL SIGNS

BP (mmHg):_____/_____ HR (bpm):_____ RR (/min):_____

INCLUSION / EXCLUSION CRITERIA (see page 4 for details)

Atrial Fibrillation?	◯Yes	◯No	
Exclusion Criteria	Under 18 Years Old?	◯Yes	◯No
	Previously Enrolled in This Study?	◯Yes	◯No
	Pregnant?	◯Yes	◯No
	Allergic to Study Medication	◯Yes	◯No
	Unstable Clinical Condition	◯Yes	◯No
	Current episode Unknown or >48hrs	◯Yes	◯No

IF ANSWER TO ANY EXCLUSION CRITERION IS YES, STOP HERE.

TIMES (24 hour clock)

Triage Time: _____ EP Time: _____ Admission/Discharge Time:_____

Previous History of Atrial Fibrillation?	◯Yes	◯No	
Previous Successful Treatment?	◯Yes	◯No	
If Yes, which method(s)	◯Rate Control	◯Drugs	◯Electrical

Duration of Current Episode (hours before EP time):_____

Current Medications_____

Other Past History ◯Yes ◯No

If Yes: Coronary Artery Disease	◯Yes	◯No	◯Not Mentioned
Valvular Heart Disease	◯Yes	◯No	◯Not Mentioned
Hypertension	◯Yes	◯No	◯Not Mentioned
CVA	◯Yes	◯No	◯Not Mentioned
Diabetes	◯Yes	◯No	◯Not Mentioned
Thyroid Disease	◯Yes	◯No	◯Not Mentioned
Thrombo-Embolism	◯Yes	◯No	◯Not Mentioned
Congestive Heart Failure	◯Yes	◯No	◯Not Mentioned
Other	◯Yes	◯No	◯Not Mentioned

(specify):_____

 Subject Number:_____

EMERGENCY DEPARTMENT TREATMENT OF ATRIAL FIBRILLATION

Rate Control Medications Given? ◯Yes ◯No

If Yes: Diltiazem ◯Yes ◯No Route____ Dose (mg):_____

Verapamil ◯Yes ◯No Route____ Dose (mg):_____

Beta-blocker ◯Yes ◯No

(specify):_____ Route____ Dose (mg):_____

Other ◯Yes ◯No

(specify):_____ Route____ Dose (mg):_____

Complications? ◯Yes ◯No

If Yes: SBP<90mmHg ◯Yes ◯No

Allergic Reaction ◯Yes ◯No

HR<60 bpm ◯Yes ◯No

AV Block ◯Yes ◯No

If Yes: ◯1° ◯2° ◯3°

Ventricular Arrhythmia ◯Yes ◯No

Other ◯Yes ◯No

(specify):_____

Spontaneous Cardioversion? ◯Yes ◯No

Pharmacological Cardioversion Drugs Given? ◯Yes ◯No

If Yes: Procainamide ◯Yes ◯No Route____ Dose (mg):_____

Other ◯Yes ◯No

(specify):_____ Route____ Dose (mg):_____

Complications? ◯Yes ◯No

If Yes: SBP<90mmHg ◯Yes ◯No

Allergic Reaction ◯Yes ◯No

HR<60 bpm ◯Yes ◯No

AV Block ◯Yes ◯No

If Yes: ◯1° ◯2° ◯3°

Ventricular Arrhythmia ◯Yes ◯No

QRS Widening ◯Yes ◯No

Other ◯Yes ◯No

(specify):_____

Full Dose Given ◯Yes ◯No

Successful? ◯Yes ◯No

 Subject Number:_____

EMERGENCY DEPARTMENT TREATMENT OF ATRIAL FIBRILLATION

Electrical Cardioversion Attempted? ◯Yes ◯No

Sedation Drug Given

Propofol	◯Yes	◯No	Route____	Dose (mg):_____
Midazolam	◯Yes	◯No	Route____	Dose (mg):_____
Fentanyl	◯Yes	◯No	Route____	Dose (mg):_____
Morphine	◯Yes	◯No	Route____	Dose (mg):_____
Other	◯Yes	◯No		
(specify):_____			Route____	Dose (mg):_____

Complications? ◯Yes ◯No

If Yes: SBP<90mmHg	◯Yes	◯No	
Allergic Reaction	◯Yes	◯No	
HR<60 bpm	◯Yes	◯No	
AV Block	◯Yes	◯No	
If Yes:	◯1°	◯2°	◯3°
Ventricular Arrhythmia	◯Yes	◯No	
Hypoxia	◯Yes	◯No	
Apnea	◯Yes	◯No	
Other	◯Yes	◯No	

(specify):_____

Cardioversion Attempt 1: _____J	Successful	◯Yes	◯No
If No: Attempt 2: _____J	Successful	◯Yes	◯No
If No: Attempt 3: _____J	Successful	◯Yes	◯No
If No: Attempt 4: _____J	Successful	◯Yes	◯No

Complications? ◯Yes ◯No

If Yes: SBP<90mmHg	◯Yes	◯No	
Allergic Reaction	◯Yes	◯No	
HR<60 bpm	◯Yes	◯No	
AV Block	◯Yes	◯No	
If Yes:	◯1°	◯2°	◯3°
Ventricular Arrhythmia	◯Yes	◯No	
Hypoxia	◯Yes	◯No	
Apnea	◯Yes	◯No	
Thrombo-Embolism	◯Yes	◯No	
Other	◯Yes	◯No	

(specify):_____

 Subject Number:_____

EMERGENCY DEPARTMENT TREATMENT OF ATRIAL FIBRILLATION

Cardiac Enzymes Ordered? ◯Yes ◯No

If Yes: CK ◯Yes - Positive ◯Yes - Negative ◯No

CK-MB ◯Yes - Positive ◯Yes - Negative ◯No

Troponin T ◯Yes - Positive ◯Yes - Negative ◯No

Post-conversion ECG done? ◯Yes ◯No

If yes: Abnormal? ◯Yes ◯No

Consultations in the Emergency Department? ◯Yes ◯No

If Yes: Anesthesia ◯Yes ◯No

Cardiology ◯Yes ◯No

Internal Medicine ◯Yes ◯No

Other ◯Yes ◯No

(specify):_____

Patient Admitted? ◯Yes ◯No

Outpatient Consultations Ordered/Advised? ◯Yes ◯No

If Yes: Cardiology ◯Yes ◯No

Internal Medicine ◯Yes ◯No

Family Physician ◯Yes ◯No

Other ◯Yes ◯No

(specify):_____

Atrial Fibrillation is to be determined by the emergency physician's assessment of the ECG.

Study medications include -rate control agents (beta-blockers, calcium-channel blockers0
-conversion agents (procainamide)
-sedation agents (propofol, midazolam, fentanyl, morphine)

Unstable medical condition includes cases of CHF, cardiac ischemia, decreased level of consciousness, or hypotension where the physician feels that emergency cardioversion is required. Cases where the physician does not feel that emergency cardioversion is required are NOT unstable.

Current episode refers to the length of time that the atrial fibrillation has been occurring. If it is greater than 48 hours or is unknown, answer yes and stop.

 Subject Number:_____

EMERGENCY DEPARTMENT TREATMENT OF ATRIAL FIBRILLATION

FOLLOW-UP INTERVIEW

Given Outpatient Appointment? ◯Yes ◯No
Made Outpatient Appointment? ◯Yes ◯No
Kept Appointment ◯Yes ◯No
Any Treatment? ◯Yes ◯No If yes, specify:_____
Given Prescription? ◯Yes ◯No If yes, specify drug:_____

Recurrence of Atrial Fibrillation? ◯Yes ◯No
Did Patient See MD for this? ◯Yes ◯No
If Yes, who? F/P ◯Yes ◯No
Cardiologist ◯Yes ◯No
Internist ◯Yes ◯No
Walk-In ◯Yes ◯No
ED ◯Yes ◯No
Other ◯Yes ◯No
specify:_____
Any Treatment? ◯Yes ◯No If yes, specify:_____
Given Prescription? ◯Yes ◯No If yes, specify drug:_____

See MD at all? ◯Yes ◯No
If yes, Why?_____
Who? F/P ◯Yes ◯No
Cardiologist ◯Yes ◯No
Internist ◯Yes ◯No
Walk-In ◯Yes ◯No
ED ◯Yes ◯No
Other ◯Yes ◯No
specify:_____
Any Treatment? ◯Yes ◯No If yes, specify:_____
Given Prescription? ◯Yes ◯No If yes, specify drug:_____

Symptoms? ◯Yes ◯No
If yes: Palpitations ◯Yes ◯No
Lightheaded ◯Yes ◯No
SOB ◯Yes ◯No
Fatigue ◯Yes ◯No
Chest Pain ◯Yes ◯No
LOC ◯Yes ◯No
CVA ◯Yes ◯No

SF-36

Wiling to Participate in Trial? ◯Yes ◯No

APPENDIX D. STRUCTURED INTERVIEW

Hello, may I please speak with _____.

Hi, my name is Melodie Mortensen. I'm a nurse at the Ottawa Hospital emergency department and I'm calling about your visit to the {Civic/General} emergency department four weeks ago.

I'm working with Dr. Atul Kapur, one of the emergency doctors, and I would like to ask you some questions about your health since that visit. It will take about 15 minutes. You can decide whether to answer any questions or all of them, it will not affect your future care. Can I ask you these questions?

WHY ARE YOU ASKING? We are interested in the care you received for the irregular heart rhythm when you came to the emergency department. Your answers will help us to evaluate the results of the treatment you received.

HOW DID YOU GET MY NUMBER/NAME? We are emergency department staff and we reviewed our charts to find patients who came in with atrial fibrillation. This has been reviewed and approved by the Ethics Board of the Ottawa Hospital.

1) When you left the emergency department were you given an appointment time or told to make an appointment with another doctor?

2) Did you make an appointment?

IF ANSWERS TO 1 AND 2 ARE BOTH 'NO' THEN SKIP TO 4.

3) Did you keep that appointment? *IF 'NO' THEN SKIP TO 4.*

3a) Were you given any treatment during that appointment?

3b) Did you receive a prescription at that appointment? *IF YES*: What was/were the drug(s) prescribed?

4) Has the atrial fibrillation / heart rhythm problem occurred again since you left the emergency department four weeks ago? *IF 'NO' SKIP TO 5.*

4a) Did you see a doctor about this? *IF 'NO' SKIP TO 5.*
4b) Who did you see / What type of doctor is he/she?
4c) Were you given any treatment at that visit?
4d) Did you receive a prescription? *IF YES*: What was/were the drug(s) prescribed?

5) Have you seen a doctor for any reason since you left the emergency department four weeks ago? *IF 'NO' SKIP TO 6.*

5a) Why?
5b) Who did you see / What type of doctor is he/she?
5c) Were you given any treatment at that visit?
5d) Did you receive a prescription? *IF YES*: What was/were the drug(s) prescribed?

6) Have you had any symptoms or medical problems since you left the emergency department four weeks ago? *IF YES, GO THROUGH LIST.*

7) Administer SF-36.

8) We are thinking of doing a study to compare the treatment you received in the emergency department four weeks ago with other treatments for your atrial fibrillation / heart rhythm problem. If you had to come in for this problem again, would you be willing to participate in a study where your treatment would decided by the study team?