Determining a protocol: rate versus rhythm control in atrial fibrillation - a quality of life study.

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Determining a protocol for treatment: Rate versus Rhythm Control in Atrial Fibrillation – a Quality of Life Study.

Samuel Dogbey
And
Marlea Lee

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**Abstract**

In the United States alone, approximately 6 million people are estimated to have atrial fibrillation (AF). Those with AF are at a dangerously high risk for the development of stroke and/or death from emboli that form secondary to the deadly arrhythmia. Much controversy exists in the medical field surrounding the best way to treat AF to reduce both the associated morbidity and mortality. This study sought to bring clarity to the controversy by analyzing clinical trials comparing rhythm control vs. rate control of atrial fibrillation. Three studies were used to evaluate which method better increased quality of life for those with AF. In general, there was no clinically statistical difference in the improvement of morbidity or mortality, and thus quality of life, between medical rate and rhythm control; though there may be trend towards rhythm control in certain instances. In conclusion, the ultimate choice of which treatment method to use rests heavily on each individual presentation of atrial fibrillation and what is best for the patient specifically.

**Introduction**

According to the Centers for Disease Control and Prevention, atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, accounting for about 15% of all arrhythmias. Nation-wide, between 2.7 and 6.1 million people are estimated to have this arrhythmia. Though atrial fibrillation may be asymptomatic, it is associated with significant morbidity and mortality, as it increases the risk of death and stroke, 2-fold and 4-5-fold respectively. The two major risk factors for developing AF are hypertensive heart disease and atherosclerotic cardiovascular disease. Other causes include alcohol intake, surgery, electrocution, myocarditis, pulmonary embolism, other pulmonary diseases, and hyperthyroidism. Successful treatment of these underlying causes typically results in resolution of the AF.

Atrial fibrillation is notorious for thrombus development due to the failure of the heart to efficiently pump blood - resulting in blood stasis and clot formation. When emboli become dislodged, typically from the left atrial appendage, they can occlude parts of the brain, gut or other peripheral circulation, resulting in clinical consequences such as: stroke, mesenteric ischemia, and other embolic phenomena respectively. AF can also cause (or worsen) heart failure, often manifesting as decreased exercise tolerance, syncope, shortness of breath or chest pain. In addition to these health related quality of life issues, AF can have socio-economic consequences. Patients often have to be on anticoagulant therapy that requires lifelong follow up and accompanying heavy financial burden. In the US, the average annual cost
attributable to the management of chronic AF to the individual is estimated at $8700, and to the nation, about $6 billion.¹

AF is classified according to the time period of occurrence, as new–onset, paroxysmal (beginning and ending abruptly, usually lasting hours to less than 7 days), persistent (lasting longer than 7 days) or permanent (when a clinical decision is made to not pursue rhythm change but to control the rate only)⁴. AF often presents with an abnormally fast heart rate, even at rest. Such patients are usually symptomatic and the heart rate must be controlled. A typical heart rate goal is below 100 beats per minute, but the optimal heart rate depends on patient subpopulation. Once an optimal heart rate is achieved, the decision has to be made for long-term management.³ Management of persistent/chronic AF may involve conversion to sinus rhythm (with drugs or electricity or both), or controlling the rate as in permanent AF. The decision to choose either management pathway depends on many factors, but general guidelines exist that help decide what treatment modality would produce optimal results for the patient. This research project is a comparative analysis of rate and rhythm control, and the health related quality of life implications to the patient, using three different studies that look at various aspects of AF and common comorbidities. Among the three studies analyzed, the specific endpoints measured and compared were all-cause mortality, cardiovascular mortality, arrhythmic/sudden death, ischemic stroke, systemic embolism, major bleeding, health-related quality of life (HRQoL), symptoms, left ventricular systolic function, exercise tolerance, and basic hematology and biochemistry lab work.

**Scenario:** A 70 year old male presents to the clinic with shortness of breath, chest pain, and an episode of syncope. The patient was found to now have comorbid heart failure. He was previously diagnosed with atrial fibrillation in 2014 and is currently on a regimen of warfarin and atenolol. After management of the patient’s current symptoms, the patient would like to know how the treatment of his atrial fibrillation will change.

<table>
<thead>
<tr>
<th>P</th>
<th>Patient/ population</th>
<th>Patients with persistent atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Intervention</td>
<td>Rhythm control</td>
</tr>
<tr>
<td>C</td>
<td>Comparison</td>
<td>Rate control</td>
</tr>
<tr>
<td>O</td>
<td>Outcome</td>
<td>Quality of Life</td>
</tr>
</tbody>
</table>

**Clinical Question:** Among patients with persistent atrial fibrillation, does rhythm control result in a better quality of life than rate control?
Methods

An initial literature search was performed using PubMed and Google Scholar and the terms “atrial fibrillation rate versus rhythm” and “rate rhythm atrial fibrillation” respectively. Inclusion criteria was limited to randomized control trials involving patients with atrial fibrillation, and including the comparison of rate control and rhythm control. Studies were excluded if they were not in English, were performed before 2005, involved animals, or if they involved comorbid diseases. Studies were further excluded based on the outcome assessment used. See flow chart (see Appendix A). Ten articles were assessed for application. Seven were excluded, because they were meta-analysis and not original studies. Three studies were included in this literature review:

A. Health-related quality of life in patients with atrial fibrillation treated with rhythm control versus rate control. Andrew et al\textsuperscript{5}.

B. Rate versus rhythm control in atrial fibrillation and clinical outcomes: Updated systematic review and meta-analysis of randomized controlled trials. Caldeira et al\textsuperscript{6}.

C. A randomized controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure (CAFÉ-II Study). Shelton et al\textsuperscript{7}.

Results

Study A

Health-Related Quality of Life in Patients with Atrial Fibrillation Treated with Rhythm Control versus Rate Control. Andrew et al\textsuperscript{5}.

Objective

The objective of this study was to assess patients’ perception of their quality of life after being treated with medical rate or rhythm control for 1 year.

Study Design

Researchers conducted an international, prospective cohort study of patients newly diagnosed with atrial fibrillation (< 1 year onset), found through the Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation or RECORD-AF database. Patient recruitment was conducted from May 2007 until April 2008 and included 5,604 patients from 21 countries in Europe, North and South Americas, and Asia.

Patients were assigned to a treatment group as determined by a treating cardiologist at a baseline visit. Rhythm control was described as antiarrhythmic drugs including class I, sotalol, or other class III. Rate control was defined as the use of an AV nodal blocker to include a non-sotalol beta-blocker, calcium channel blocker, or digoxin. The baseline characteristics (See Appendix B) of the cohorts were assessed with a propensity score model. The model was used
to determine the likelihood that a patient would fall into a particular treatment cohort prior to assignment; this was done to decrease confounding due to covariates.

The researchers hypothesized that improvements in quality of life would be seen in both cohorts, but thought that the magnitude of improvement in the rhythm cohort would be greater than that of the rate cohort. To assess quality of life (QoL), the University of Toronto Atrial Fibrillation Severity Scale (see Appendix C) was given at baseline, 3 months, and 1 year. The questionnaire included patient-reported information about seven atrial fibrillation-related symptoms assigned a severity score from zero to five, five being the most severe. Scores total from 0-35 with higher values indicating a worse patient perception of quality of life secondary to atrial fibrillation.

The primary outcome measured was the difference in the QoL reported from baseline to 1 year. Results were analyzed per protocol with patients who died during the study, those with incomplete questionnaires at baseline or 12 months, and those needing to change treatment prior to the study conclusion, excluded from the study results. The results were analyzed using Student t tests – a method that compares the averages of study groups to find any statistically significant differences.\(^8\)

**Results**

After exclusions, 2,439 patients were sorted into rate and rhythm control cohorts (containing 1,267 and 1,172 patients respectively). At baseline, the mean Atrial Fibrillation Severity Scale (AFSS) score was the same in both cohorts (See Table 1). At 12-months, AFSS decreased, or improved, by 2.82 points in the rhythm cohort, while the rate cohort saw an improvement, or decrease, in AFSS score by 2.11 points. The improvements showed statistical significance with a p-value <0.01.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Mean AFSS Score at Baseline</th>
<th>Mean AFSS Score at 12-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>8.7 ± 7.0</td>
<td>6.5</td>
</tr>
<tr>
<td>Rhythm</td>
<td>8.7 ± 7.0</td>
<td>5.8</td>
</tr>
</tbody>
</table>

*Table 1: Table shows average Atrial Fibrillation Severity Scale (AFSS) scores of the cohorts at baseline and at the final 12-month follow up.*

While the results statistically favor rhythm control, the researchers proposed that there was also clinical significance in the findings. The researchers correlated an improvement in QoL by ~3 points, as demonstrated by the rhythm cohort, to an improvement by one class in the Canadian Cardiovascular Society Severity of Atrial
Fibrillation or CSS-SAF⁹. The CCS-SAF is a clinical tool used to assess atrial fibrillation severity based on patient symptoms and impact on QoL (see Appendix D). The impact of symptoms on patient functionality dictates which class of atrial fibrillation severity they fall into; class 0 being the least severe, class 4 being the most severe⁹. The researchers suggested that the improvements in QoL of the rhythm control group after 12 months were associated with decreased atrial fibrillation related emergency room visits and hospitalizations. Thus suggesting that treating atrial fibrillation with rhythm control drugs would decrease healthcare related costs associated with emergency room visits and hospitalizations⁵.

In addition to the results of the study objective, the researchers also assessed the improvement of quality of life in the subgroups of those with paroxysmal AF and those with comorbid heart failure and AF. In the 1,255 patients with paroxysmal AF at baseline, 780 and 475 were assigned to the rhythm and rate cohorts respectively. A trend toward rhythm control was demonstrated by the greater improvement (0.94 point) of AFSS scores between rhythm and rate cohorts at 12-month follow up (See Table 2). Among the 400 patients diagnosed with AF and heart failure at baseline (170 rhythm cohort, 230 rate cohort), the researchers observed no statistically significant difference between AFSS scores at 12-months - as indicated by the p-value (0.40); there were however, general improvements of AFSS scores in this comorbid subgroup.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Cohort</th>
<th>AFSS Improvement seen at 12-months (points)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal AF</td>
<td>Rate</td>
<td>1.57</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Rhythm</td>
<td>2.51</td>
<td></td>
</tr>
<tr>
<td>AF and Heart Failure</td>
<td>Rate</td>
<td>2.68</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>Rhythm</td>
<td>2.02</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Table shows the amount of improvement (or decrease) in Atrial Fibrillation Severity Scale scores at 12-month from baseline averages and p-values analyzing the statistical significance of the differences between the two cohorts.

**Study B**

*Rate versus rhythm control in atrial fibrillation and clinical outcomes: Updated systematic review and meta-analysis of randomized controlled trials. Caldeira et al⁶.*
Objective
The study objective was to compare the clinical efficacy of rate and rhythm strategies in patients with AF not due to cardiac surgery.

Study Design
This study, involving a total of 7,499 participants with AF, is a systematic review and meta-analysis of 8 randomized controlled trials (comparing rate and rhythm control strategies), retrieved by systematic search of PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) databases. Keywords used in the search were: rate, beta-blocker, acebutolol, atenolol, bisoprolol, carvedilol, esmolol, metoprolol, nadolol, pindolol, propranolol, timolol, calcium-channel blocker, verapamil, diltiazem, digitalis, digoxin, rhythm, amiodarone, sotalol, propafenone, disopyramide, dofetilide, flecainide, ibutilide, dronedarone and azimilide, mortality, death, stroke, embolism, thromboembolic, thromboembolism, bleeding and atrial fibrillation. Boolean operators “AND” and “OR” were used to combined search terms. Postoperative and post-percutaneous intervention studies were excluded using the Boolean operator “NOT”. Other inclusion criteria were randomized control trials (RCTs) comparing pharmacological approaches to maintaining rate or rhythm control in patients with AF, studies with mean participant age greater than 55 years and studies that had intention to treat (ITT) analysis (or provided data for its calculation). Quasi-randomized studies and prospective cohort studies were excluded. Selected studies were assessed by one review author and then reassessed by another. Data was retrieved and analyzed using the RevMan software version 5.1.4 (for pooled data) and the Mantel-Haenszel method (for dichotomous outcomes). Then relative risk and 95% CI calculated. The specific end-points measured and compared were: all-cause mortality, cardiovascular mortality, arrhythmic/sudden death, ischemic stroke, systemic embolism and major bleeding. In all the selected trials, interventions were unblinded to physicians and patients.

Results
With these selection criteria, 8 studies were selected for analysis (PIAF, RACE, AFFIRM, STAF, HOT CAFÉ, AF-CHF, J-RHYTHM and CAFÉ-II studies). The mean age of the patients in the selected studies was 68 years and majority were men in all the trials included (63.4-82.0%). The length of follow-up ranged from 1- 3.5 years with a weighted mean follow up duration of 2.9 years. Prevalence of hypertension ranged from 42.8% to 64.3%, coronary artery disease 7.4% to 43.5% and valvular disease from 4.9% to 17%. Two of the studies (AF-CHF and CAFÉ-II) included only patients with heart failure (100% heart failure prevalence) whereas 1 study (PIAF) provided no heart failure data. In-between, heart failure prevalence ranged from 3.6% to 70%. Three of the studies (AFFIRM, AF-CHF and J-RHYTHM) had cross over rates greater than 15%.
All-cause mortality, cardiovascular mortality, arrhythmic/sudden death, ischemic stroke, systemic embolism and major bleeding were all found to be similar for both rate and rhythm control groups in all the selected studies, and also when all data are pooled in the meta-analysis. There were observed differences between the two treatment groups in some of the trials, howbeit, not statistically significant. These “statistically insignificant” differences may however, have clinical significance for specific sub-populations. For instance, in the AFFIRM trial (which together with the AF-CHF trial contributed most of the data), arrhythmia/sudden death incidence was lower in the rhythm control group, making rhythm control possibly a better strategy than rate control when considering risk of death from fatal arrhythmias. Also, in most of the studies the rate control group showed less ischemic stroke and systemic embolism, though not statistically significant. Another observation is that analysis of trials with mean age less than 65 years revealed better outcomes for the rate control group.

It is noteworthy that all-cause mortality included both cardiovascular and noncardiovascular mortality. In the AFFIRM study pulmonary diseases (especially pneumonia) and lung cancer constituted the majority of non-cardiovascular deaths. Death rate due to amiodarone toxicity was calculated, because amiodarone was prescribed to most patients in 4 of the 6 trials (see table 2) reporting data on antiarrhythmic drug use. Though death due to amiodarone toxicity was relatively low (3 out of 39 pulmonary deaths in the rhythm control group), its calculation was deemed important since amiodarone is prescribed much longer than the average duration of the studies, and therefore likely to result in a higher mortality rate than the meta-analysis revealed. The results from individual studies are summarized in Tables 3 and 4. Figures 1 and 2 represent the forest plots for all-cause and cardiovascular mortality respectively.

From Table 3, it can be inferred that all outcomes showed no statistical heterogeneity (except Ischemic stroke which showed $I^2$ of 26%). Since statistical heterogeneity was initially defined as $I^2$ of greater than 50%, outcomes were assumed to show no statistical heterogeneity. However, relative risk computations were based on random effects model since there was significant clinical heterogeneity among study participants (generally, relative risks are computed using the fixed effects model if study groups show no significant heterogeneity, and random effects model is used if significant heterogeneity exists). To demonstrate that the selection of either random or fixed effects model to compute relative risks made no statistical difference in the interpretation of the outcomes (since all confidence intervals included 1), relative risk computations using the fixed effects model are presented side-by-side with those of the random effects model for easy comparison. Another observation from Table 3 is that the confidence intervals that were used were different for each of the outcomes, and exactly what informed the choice of these specific confidence intervals is unclear. Since confidence intervals
determine whether or not the calculated relative risk is statistically significant, an explanation of how the various confidence intervals were arrived at would have added more clarity to the interpretation of the results.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>Patients</th>
<th>Rate</th>
<th>Rhythm</th>
<th>Random Effects (RR [95% CI])</th>
<th>Fixed Effects (RR [95% CI])</th>
<th>Heterogeneity I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>8</td>
<td>7499</td>
<td>3738</td>
<td>3761</td>
<td>0.95 [0.85-1.05]</td>
<td>0.94 [0.84-1.04]</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>7</td>
<td>6676</td>
<td>3334</td>
<td>3342</td>
<td>0.99 [0.87-1.13]</td>
<td>0.99 [0.87-1.13]</td>
<td>0</td>
</tr>
<tr>
<td>Arrhythmic/sudden death</td>
<td>5</td>
<td>6410</td>
<td>3202</td>
<td>3208</td>
<td>1.12 [0.91-1.38]</td>
<td>1.12 [0.91-1.38]</td>
<td>0</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>4</td>
<td>5288</td>
<td>2632</td>
<td>2656</td>
<td>0.89 [0.52-1.53]</td>
<td>0.92 [0.70-1.23]</td>
<td>26</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>6</td>
<td>6062</td>
<td>3013</td>
<td>3049</td>
<td>0.89 [0.69-1.14]</td>
<td>0.88 [0.68-1.12]</td>
<td>0</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5</td>
<td>5810</td>
<td>2888</td>
<td>2922</td>
<td>1.10 [0.89-1.36]</td>
<td>1.10 [0.89-1.36]</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3: Depicts no statistical difference between the two groups (rate versus rhythm) with regards to all-cause mortality, cardiovascular mortality and mortality due to fatal arrhythmias. The same holds true for all other events measured. CI: confidence interval; RR: risk ratio

<table>
<thead>
<tr>
<th></th>
<th>PIAF</th>
<th>RACE</th>
<th>AFFIRM</th>
<th>STAF</th>
<th>HOT CAFÉ</th>
<th>AF-CHF</th>
<th>J-RHYTHM</th>
<th>CAFÉ II</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Amiodarone in rhythm control group</td>
<td>100</td>
<td>N/A</td>
<td>62.8</td>
<td>42</td>
<td>56.7</td>
<td>82</td>
<td>0.5</td>
<td>80</td>
</tr>
</tbody>
</table>

Table 4: Shows the percentage of patients in the various RCTs who received Amiodarone as the antiarrhythmic. With the exception of the RCTs J-Rhythm and STAF in which less than half of the patients received amiodarone, all in all other trials (except RACE) majority of patients received amiodarone. No amiodarone data was available for the RACE trial.
Figure 1: Forest plot of all-cause mortality. The risk ratios (in the given confidence intervals) for individual studies, and the composite data all show no statistically significant difference between the two groups (rate and rhythm control groups)\(^6\).

Figure 2: Forest plot of cardiovascular mortality. The relative risks (in the given confidence intervals) for individual studies, and the composite data all show no statistically significant difference between the two groups (rate and rhythm control groups)\(^6\).

**Study C**

*Randomized, controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure (CAFÉ-II Study).* Shelton et al\(^6\).
Objective

The objective of the study was to investigate whether restoring sinus rhythm could improve cardiac function, symptoms, exercise capacity, and quality of life (QoL) in patients with chronic heart failure.

Study Design

The study was a RCT involving 61 patients with chronic AF and heart failure. Other inclusion criteria were age 18 years and older and symptomatic heart failure of NYHA Class II or worse with evidence of systolic dysfunction on echocardiography. Patients with contraindication to oral anticoagulants were excluded. The patients were randomly assigned to one of two groups—rate control group and rhythm control group. The rhythm control group was given at least 3 months of amiodarone prior to biphasic electrical cardioversion. Once sinus rhythm was successfully achieved, they were then continued on long-term amiodarone, in addition to beta-blocker and/or digoxin to keep heart rate <80 bpm at rest and <110 bpm after walking. The rate control group was treated with only beta-blocker and/or digoxin to achieve the above heart rates. Both groups received chronic anticoagulation throughout the study unless contraindications developed. All patients had their heart failure treatment optimized.

Symptoms, walk distance (6-minute corridor walk test, or 6MWT), QoL and cardiac function were assessed at baseline and 1 year. To assess these parameters, patients were examined, had 12-lead EKG, 2-dimensional echocardiography, had blood drawn for standard hematology and biochemistry profiles, and NT-proBNP determination. NT-proBNP is the N-terminal amino acid sequence cleaved in vivo from the prohormone (proBNP), and is used to quantify/compare left ventricular dysfunctions (the higher the blood level of NT-proBNP, the worse the left ventricular function). Though the authors did not clearly state the purpose of NT-proBNP measurements, they may have been used to supplement the comparison of left ventricular dysfunction which was mainly qualitative (i.e. NT-proBNP can serve as a semi-quantitative measure in the comparison of the two groups).

Patients were reviewed at four monthly intervals. During each review cardiovascular events were recorded and a 12-lead EKG obtained. Rate control at rest and during a 6-minute corridor was performed. At 1 year the above routines were done in addition to a 2-D echocardiography and blood drawn. QoL was assessed by having patients fill out a generic questionnaire (the Medical Outcomes Study Short Form-36, SF-36) and a disease specific questionnaire (the Minnesota Living With Heart Failure questionnaire, MLWHF). Left ventricular (LV) function was assessed qualitatively on a 6-point scale as normal, mild, mild-to-moderate, moderate, moderate-to-severe and severe; this was done because of the difficulty associated with measuring ejection fraction in AF. The primary outcome measured was QoL at 1 year.
Secondary outcomes were proportion in sinus rhythm (SR), MLWHF, NT-proBNP, 6MWT and severity of LV systolic dysfunction. All analyses were based on intention-to-treat.

Results

Of the 61 patients, 31 were randomly assigned to the rate control group and 30 to the rhythm control group. The median duration of AF was 14 months. Before randomization most patients were already receiving beta-blockers (80%), ACE inhibitors (89%) and loop diuretics (90%). Two patients died (one from each group) during follow-up. Warfarin was discontinued in 1 person (from the rate control group) due to recurrent epistaxis, and 1 person (also from the rate control group) underwent elective pacemaker insertion due to bradycardia.

At baseline 61% of the rate control group was already at the target resting heart of <80 bpm and post-exercise target heart rate of <110 bpm. The mean ventricular rate at rest was 73 bpm, post-exercise was 100 bpm at baseline. By 1 year the mean resting heart rate had dropped to 70 bpm and post-exercise heart rate also had dropped to 87 bpm. Also 65% and 84% of the rate control group were already on digoxin and beta-blocker respectively at baseline. At 1 year 84% and 90% were on digoxin and beta-blocker respectively.

For the rhythm control group beta-blocker use at baseline and at 1 year were 83% and 93% respectively. Amiodarone was started in all patients in the rhythm control group and at 1 year 24 (80%) patients were still on amiodarone. Cardioversion restored sinus rhythm in 18 of 23 (78%) patients in whom it was attempted. One person declined electrical cardioversion and remained in AF throughout the study. Four patients required a second electrical cardioversion due to AF recurrence. Overall, 26 (87%) patients were converted from AF to SR at some point during the study. The prevalence of AF in the rhythm control group was 53% at 4 months, 30% at 8 months and 34% at 1 year. At 1 year 6 (20%) patients had crossed over to the rate control group.

Regarding QoL, patients in the rhythm control group showed a greater improvement when SF36vII was used (See Figures 3 and 4). When MLWHF was used, the difference in QoL was not statistically significant. However, a post-hoc analysis which compared only the rhythm control patients able to achieve sinus rhythm to the rate control group showed superior results in favor of the rhythm control with both SF36vII and MLWHF questionnaires. A post-hoc analysis is a statistical analysis performed after the study is concluded. It is termed post-hoc because it was not included in the initial planning of the study; simply put, it is taking a second look at the data to see what else might be found. The NYHA class remained the same between baseline and 1 year, and there was no difference between the two treatment strategies (rate versus rhythm control).
Figure 3. Comparison of change in QoL scores over 1 year between rate and rhythm control groups. The p values denote the comparison between groups. Bars represent mean QoL score and whiskers represent the standard error of the mean. *Inverse Minnesota Living with Heart Failure (MLWHF) score; unlike SF-36 vll, a lower score indicates a better QoL.

Figure 4. Comparison of change in QoL scores over 1 year between rate and rhythm control groups (comparing only those who maintained SR in the rhythm control groups with those achieving adequate rate control in rate control group). Bars represent mean QoL score, and whiskers represent the standard error of the mean. *Inverse Minnesota Living with Heart Failure (MLWHF) score; unlike SF-36 vll, a lower score indicates a better QoL.

6MWT distances at baseline for rate and rhythm control groups were respectively 307 meters and 352 meters. At 1 year the respective 6MWT distances were 311 meters and 368 meters (See Figure 5). Comparing the patients in rate control group who achieved adequate
rate control with the patients in the rhythm control group who achieved sinus rhythm, the mean changes in 6MWT distance were -10 meters and +21 meters respectively.

![Graph showing 6MWT distance at baseline and 1 year.](image)

**Figure 5.** Six minute walk test distance at baseline and 1 year.

At baseline, LV function was designated as “moderately” impaired for both groups. The rhythm control group achieved a greater improvement in LV function at 1 year compared to the rate control group- the median severity of LV systolic dysfunction at 1 year in the rhythm control group improved from “moderate” to “mild” while the parameter remained “moderate” in the rate control group.

NT-proBNP was similar (not statistically significant) for both groups at baseline. For rate control group median was 1835 pg/ml (ranged from 947 to 2546). For the rhythm control group the median was 1285 pg/ml (ranged from 913 to 1624). At 1 year the median NT-proBNP for rate control group was 1480 pg/ml (1074 to 2681) and for rhythm control group was 685 pg/ml (347 to 1176). Over the 1 year period a comparatively greater reduction in NT-proBNP was seen in the rhythm control group than the rate control group (-0.03 vs -0.23log [NT-proBNP] for rate and rhythm control respectively). The greatest reduction in (median) NT-proBNP over the 1 year period was seen in those patients maintaining SR (1472 to 458 pg/ml).

For the hematology and biochemistry data, there was about 1.0 g/dl reduction in hemoglobin (Hgb) over 1 year in the rhythm group (14.2 at baseline to 13.4 at 1 year). Creatinine (Cr) increased by 18.5 micromol/L (from baseline of 105 to 121 at 1 year). On the other hand there was no significant change in the corresponding data for the rate control group (baseline Hgb 13.5 vs Hgb at 1 year 13.2; baseline Cr of 118.8 vs Cr at 1 year 18.8). Although the
fall in the hemoglobin and the rise in creatinine respectively, in the rhythm control group at 1 year were statistically significant, their clinical significance was not clearly discussed in the article. However, a possible significance would be that they may have resulted from side effects of the antiarrhythmics used. If this is so, then the changes represent a disadvantage of rhythm control (since medication side effects are an important factor in management decisions). Thyroid Stimulating Hormone (TSH) remained fairly unchanged at baseline and at 1 year for both groups.

**Discussion**

Overall, there was no clear benefit from the choice of treatment strategy in atrial fibrillation between rhythm and rate control. There were however, trends toward rhythm control in subpopulations of patients with AF\(^5,7\) (specifically those with comorbid heart failure) and when assessing quality of life based on symptom severity\(^5\).

There were notable differences between the cohorts at baseline in Study A\(^5\). The rate control cohort was older, a greater percentage had persistent AF, and had high incidence of comorbidities: heart failure, hypertension, diabetes mellitus, and prior stroke (CHADS\(_2\)). Although these were mentioned by the researchers, it was never discussed that the differences could have negatively impacted the success of the rate cohort. It is also worth mentioning that while this study focuses on patient perception of quality of life through decreased severity and frequency of symptoms, it fails to address the major sequelae often associated with atrial fibrillation. While symptomatic control of AF is important, it must be understood that lack of, or improvement in symptoms does not necessarily equate to decreased risk of adverse events or mortality associated with AF - as it can often be asymptomatic and still associated with high morbidity and mortality\(^2\).

Strengths of this study include the addressing of the study’s limitations and assessment methods. Patients included in the study had been diagnosed up to 1 year prior, giving them time to have previously been treated before the study. The researchers propose that the success of the rhythm cohort could have been confounded by prior treatment with antiarrhythmic drugs. In addition, crossover was proposed to have had diluted patient perception of quality of life improvements upon primary analysis. It was also discussed that patients yielding the greatest improvements in quality of life were those that were more likely to have had more severe symptoms at baseline. Thus, it was concluded that severity of symptoms largely impacts perceived improvement with treatment.

Further, this study adds a different perspective to previous evaluations of rate and rhythm control of atrial fibrillation. Whereas previous studies largely assess the success of treatment based on the objective occurrence of adverse events, this study assessed treatment
success from the subjective point of view of the patient. Though it can be argued that the use of a questionnaire is too subjective, this is one of few studies that found statistically significant trends toward rhythm control; perhaps this was due to the method of analysis. When considering patient involved care, subjective studies like this are beneficial in that they take into account clinical presentation and patient point of view.

Statistically, the results of Study A were found to be significant with a p-value <0.01. However, this significance may not have clinical application in that there was only a 0.75 point difference between the final AFSS scores of the two cohorts. While the rhythm cohort did experience a greater improvement in quality of life from baseline, the minimal difference between the cohorts is borderline unremarkable. Further, the researchers originally defined clinically significant improvement as an AFSS score that decreased, or improved, by ≥3 points. Neither cohort had an overall clinically significant improvement as defined by the study itself (final rate improvement, 2.11 points; final rhythm improvement, 2.82 points). Given this interpretation of the results, it is questionable as to whether in general, rhythm control is actually better than rate control in the reduction of symptom severity and perceived improvement of quality of life in AF.

Strengths of Study B include the inclusion of randomized control trials (RCTs) only. Also the number of participants in each individual study and in the overall meta-analysis were relatively large. Another strength is that, besides the PIAF and RACE trials (that showed some differences in baseline characteristics), all the other selected studies had participants with similar baseline characteristics. This ensures homogeneity and a fair comparison of results. However, there are potential sources of error; though the studies were all RCTs, all of them were unblinded to both physicians and patients, which is a potential source of bias. One source of unblinding is the physical nature of electrical cardioversion. This could not be remedied because the use of fake electrical cardioversion to ensure blinding raised an ethical dilemma and therefore was not used. In addition, though the selected studies were considered homogenous by calculation, the statistically “insignificant” heterogeneity may, in fact, be significant in reality. Lastly, for studies that did not supply data for systemic embolism, this was calculated by adding ischemic stroke and systemic embolism, with the assumption that in AF most ischemic strokes originate from cardiac emboli. However, some ischemic strokes in AF may result from thrombosis of cerebral vessels, making this calculation likely inaccurate.

Overall, Study B results showed no statistical difference between the two treatment groups with regards to mortality (both all-cause and cardiovascular mortality). For all-cause mortality, for instance, the calculated death risk ratio was 0.95 with a 95% confidence interval of 0.86-1.05 (for random effect calculation) and relative risk of 0.94 with a 95% CI of 0.84-1.04 (using fixed effects calculation). Similarly, there was no statistical difference between the two
regarding all other outcomes measured. Besides the pooled data in the meta-analysis, each of the studies individually showed no statistical difference in mortality (both all-cause and cardiovascular mortality) and in all the other outcomes. However, when certain categories of studies were pooled together, there seems to be an urge of one strategy over the other when specific end-points were considered. For instance, when trials with at least 50% of participants with comorbid heart failure were pulled together, there was significantly lower occurrence of systemic embolic events in the rate control group. The calculated relative risk was 0.43 (95% CI: 0.21-0.89). This could be explained by the fact that heart failure is a component of the CHADS2 score, so such patients would have been on chronic anticoagulation, thereby reducing their risk of systemic embolic events. In light of the fact that the literature tends to favor rhythm control in young/middle-aged patients, the observation that analysis of trials with mean age less than 65 years revealed better outcomes for the rate control group, is unusual. This may have occurred purely by chance as the sample size involved is not representative of the general young/middle-age population.

Strengths of Study C include randomization and the fact that both groups had similar baseline characteristics. However, treatment was unblinded to both physicians and patients, and this could have affected all measured parameters (except the lab tests). Another limitation is the relatively small sample size (a total of 61 participants). Also, because only symptomatic paroxysmal AF in the rhythm control group would have been reported, asymptomatic paroxysmal AF (in the rhythm control group) in between patient visits could have been missed. This, if significantly prevalent, could have affected the parameters for the rhythm control group, and this effect was not accounted for.

Intention to treat (rather than per-protocol) analysis was used in the study, thus reducing bias. However, the downside to using intention to treat analysis is that the effect of restoring sinus rhythm in the rhythm control group could have been diluted by the inclusion of patients in whom cardioversion to sinus rhythm was unsuccessful.

The results in Study C seemed to indicate an urge of rhythm control over rate control in most of the measured outcomes. QoL, exercise performance and LV function all showed significantly larger improvements in the rhythm control group. Theoretically, improvement in left ventricular function would be expected to decrease strain in the ventricles thereby reducing NT-proBNP, and this is what was observed in the trial. However, creatinine reduced significantly more in the rate control group than the rhythm control group. This could have occurred as a result of possible nephrotoxicity of some antiarrhythmic medications; amiodarone, for example, is nephrotoxic when combined with statins, and some of these patients may have been on statins concurrently (though no data was reported on statin use).
Application to the Patient

Scenario: A 70 year old male presents to the clinic with shortness of breath, chest pain, and an episode of syncope. The patient was found to now have comorbid heart failure. He was previously diagnosed with atrial fibrillation in 2014 and is currently on a regimen of warfarin and atenolol. After management of the patient’s current symptoms, the patient would like to know how the treatment of his atrial fibrillation will change.

With the development of comorbid heart failure, the best option for treatment of this patient’s atrial fibrillation is now is rhythm control. Due to the development of comorbid heart failure despite rate control, the conclusions from the research recommend a trial of rhythm control\textsuperscript{6,7} in addition to his current regimen of warfarin and atenolol. It is important to maintain rate control in patients with atrial fibrillation, and anti-coagulation with warfarin to prevent thrombosis.

Conclusion

The decision to choose rate control or rhythm control for treatment of atrial fibrillation depends on several factors. The presence and type of comorbidities, the duration of AF, age of the patient, medication side effects, symptoms, and patient preferences must all be considered in tandem. The majority of available studies do not demonstrate a clear advantage of rhythm control over rate control or vice versa. Even so, in the ones that trend towards rhythm control, the differences in improvement seem to be small and make it difficult to confidently say that rhythm control is the best option for treatment. In addition, given the heterogeneity of the AF patient population, a “one-size-fits–all” management protocol is impractical. While these findings make it difficult to determine a general protocol for the treatment of AF, they do provide a framework that may be able to help clinicians, along with patient input, decide on which treatment method is “best”.

Appendix A: PRISMA Flow Diagram

Identification

“Atrial fibrillation rate vs rhythm” (PubMed) (n = 587)

“Rate rhythm atrial fibrillation” (Google Scholar) (n = 305,000)

Records after duplicates removed (n = 42,287)

Screening

Filters – within 15 years, humans, English language, RCT, removed “versus”, MeSH Terms – “Atrial fibrillation” and “QOL” (n = 166)

Records excluded (n = 42,121)

Eligibility

Full-text articles assessed for eligibility (n = 15)

Full-text articles excluded due to comorbid diseases, assessment of outcome, and/or study parameters (n = 12)

Included

Studies included in qualitative synthesis (n = 10)

Records excluded (n = 7)

Studies included in quantitative synthesis (meta-analysis) (n = 3)
**Appendix B**: Baseline patient demographics of Study A - *Health-Related Quality of Life in Patients with Atrial Fibrillation Treated with Rhythm Control versus Rate Control. Andrew et al⁵*.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rhythm Cohort (n=1,267)</th>
<th>Rate Cohort (n=1,172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>740</td>
<td>686</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>66.4 ± 11.8</td>
<td>68.8 ± 11.5</td>
</tr>
<tr>
<td>Systolic BP, mm Hg (mean ± SD)</td>
<td>133.2 ± 19.1</td>
<td>132.5 ± 19.7</td>
</tr>
<tr>
<td>Resting heart rate, bpm (mean ± SD)</td>
<td>75.8 ± 21.3</td>
<td>77.8 ± 18.3</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>780</td>
<td>475</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>403</td>
<td>640</td>
</tr>
<tr>
<td><strong>CHADS₂ score ≥2</strong></td>
<td>461</td>
<td>540</td>
</tr>
<tr>
<td>Antithrombotic at baseline</td>
<td>1067</td>
<td>1035</td>
</tr>
<tr>
<td>Vitamin K antagonist use</td>
<td>721</td>
<td>773</td>
</tr>
<tr>
<td>History of Heart Failure</td>
<td>170</td>
<td>230</td>
</tr>
<tr>
<td>History of AF symptoms</td>
<td>1027</td>
<td>839</td>
</tr>
<tr>
<td>Smokers (current or former)</td>
<td>546</td>
<td>520</td>
</tr>
<tr>
<td>Class I drug within the last month</td>
<td>224</td>
<td>23</td>
</tr>
<tr>
<td>β-blocker within the last month</td>
<td>661</td>
<td>846</td>
</tr>
<tr>
<td>Class III drug within the last month</td>
<td>550</td>
<td>86</td>
</tr>
<tr>
<td>CCB use within the last month</td>
<td>121</td>
<td>223</td>
</tr>
<tr>
<td>Digoxin use in the past month</td>
<td>169</td>
<td>329</td>
</tr>
<tr>
<td>AFSS score (mean ± SD)</td>
<td>8.7 ± 7.0</td>
<td>8.7 ± 7.0</td>
</tr>
</tbody>
</table>

SD indicates standard deviation; BP, blood pressure; AF, atrial fibrillation; CHADS₂ score, prior stroke; CCB, calcium channel blocker.
Appendix C: University of Toronto Atrial Fibrillation Severity Scale (questionnaire) used in Study A - Health-Related Quality of Life in Patients with Atrial Fibrillation Treated with Rhythm Control versus Rate Control. Andrew et al.⁵.
University of Toronto Atrial Fibrillation Severity Scale

7. How severe was your most recent episode of irregular heart rhythm?
   - Not at all severe
   - Extremely severe
   - 1 2 3 4 5 6 7 8 9 10

8. How severe was your first episode of irregular heart rhythm?
   - Not at all severe
   - Extremely severe
   - 1 2 3 4 5 6 7 8 9 10

PART B

9. Have you ever been cardioverted (i.e. been put to sleep and electrically shocked)?
   - Yes
   - No
   - If yes, how many times?

10. How many times did you visit the emergency room within the past year because of an irregular heart rhythm?
    - 0
    - 1
    - 2
    - 3
    - 4
    - 5
    - more than 5 times

11. How many times were you hospitalized within the past year because of an irregular heart rhythm?
    - 0
    - 1
    - 2
    - 3
    - 4
    - 5
    - more than 5 times

12. How many times did you visit your specialist within the past year because of an irregular heart rhythm?
    - 0
    - 1
    - 2
    - 3
    - 4
    - 5
    - more than 5 times

University of Toronto Atrial Fibrillation Severity Scale: revised Jan 21, 2000.
University of Toronto Atrial Fibrillation Severity Scale

PART C

Please indicate how bothered you have been by the following symptoms (if at all) in the past 4 weeks. Fill in the answer that best describes your symptoms.

1. Palpitations:
   How often have you been bothered by this symptom in the past 4 weeks?

<table>
<thead>
<tr>
<th>I have not had this symptom in the past 4 weeks</th>
<th>Very little</th>
<th>A little</th>
<th>A fair amount</th>
<th>A lot</th>
<th>A great deal</th>
</tr>
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<tbody>
<tr>
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</table>

2. Shortness of breath at rest:
   How often have you been bothered by this symptom in the past 4 weeks?

<table>
<thead>
<tr>
<th>I have not had this symptom in the past 4 weeks</th>
<th>Very little</th>
<th>A little</th>
<th>A fair amount</th>
<th>A lot</th>
<th>A great deal</th>
</tr>
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<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

3. Shortness of breath during physical activity:
   How often have you been bothered by this symptom in the past 4 weeks?

<table>
<thead>
<tr>
<th>I have not had this symptom in the past 4 weeks</th>
<th>Very little</th>
<th>A little</th>
<th>A fair amount</th>
<th>A lot</th>
<th>A great deal</th>
</tr>
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</table>

4. Exercise intolerance (fatigue during mild physical activity):
   How often have you been bothered by this symptom in the past 4 weeks?

<table>
<thead>
<tr>
<th>I have not had this symptom in the past 4 weeks</th>
<th>Very little</th>
<th>A little</th>
<th>A fair amount</th>
<th>A lot</th>
<th>A great deal</th>
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5. Fatigue at rest
   How often have you been bothered by this symptom in the past 4 weeks?

<table>
<thead>
<tr>
<th>I have not had this symptom in the past 4 weeks</th>
<th>Very little</th>
<th>A little</th>
<th>A fair amount</th>
<th>A lot</th>
<th>A great deal</th>
</tr>
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</tbody>
</table>

6. Lightheadedness/dizziness
   How often have you been bothered by this symptom in the past 4 weeks?

<table>
<thead>
<tr>
<th>I have not had this symptom in the past 4 weeks</th>
<th>Very little</th>
<th>A little</th>
<th>A fair amount</th>
<th>A lot</th>
<th>A great deal</th>
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</table>

7. Chest pain or pressure
   How often have you been bothered by this symptom in the past 4 weeks?

<table>
<thead>
<tr>
<th>I have not had this symptom in the past 4 weeks</th>
<th>Very little</th>
<th>A little</th>
<th>A fair amount</th>
<th>A lot</th>
<th>A great deal</th>
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</table>

University of Toronto Atrial Fibrillation Severity Scale: revised Jan 21, 2000.
Appendix D: Canadian Cardiovascular Society Severity of Atrial Fibrillation used in Study A - *Health-Related Quality of Life in Patients with Atrial Fibrillation Treated with Rhythm Control versus Rate Control. Andrew et al*.

### Canadian Cardiovascular Society
Severity of Atrial Fibrillation (SAF) Scale

#### Step 1 – Symptoms
Identify the presence of the following symptoms:
- Palpitation
- Dyspnea
- Dizziness, presyncope, or syncope
- Chest pain
- Weakness or fatigue

#### Step 2 – Association
Is AF, when present, associated with the above-listed symptoms (A-E)?

For example: Ascertain if any of the above symptoms are present during AF and likely caused by AF (as opposed to some other cause).

#### Step 3 – Functionality
Determine if the symptoms associated with AF (or the treatment of AF) affect the patient’s functionality (subjective quality of life).
### CCS-SAF Class Definitions

<table>
<thead>
<tr>
<th>Class 0</th>
<th>Asymptomatic with respect to AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>Symptoms attributable to AF have <em>minimal</em> effect on patient’s general QOL.</td>
</tr>
<tr>
<td></td>
<td>• minimal and/or infrequent symptoms, or</td>
</tr>
<tr>
<td></td>
<td>• single episode of AF without syncope or heart failure</td>
</tr>
<tr>
<td>Class 2</td>
<td>Symptoms attributable to AF have a <em>minor</em> effect on patient’s general QOL.</td>
</tr>
<tr>
<td></td>
<td>• mild awareness of symptoms in patients with persistent/permanent AF, or</td>
</tr>
<tr>
<td></td>
<td>• rare episodes (e.g. less than a few per year) in patients with paroxysmal or intermittent AF</td>
</tr>
<tr>
<td>Class 3</td>
<td>Symptoms attributable to AF have a <em>moderate</em> effect on patient’s general QOL.</td>
</tr>
<tr>
<td></td>
<td>• moderate awareness of symptoms on most days in patients with persistent/permanent AF, or</td>
</tr>
<tr>
<td></td>
<td>• more common episodes (e.g. more than every few months) or more severe symptoms, or both, in patients with paroxysmal or intermittent AF</td>
</tr>
<tr>
<td>Class 4</td>
<td>Symptoms attributable to AF have a <em>severe</em> effect on patient’s general QOL.</td>
</tr>
<tr>
<td></td>
<td>• very unpleasant symptoms in patients with persistent/paroxysmal AF and/or</td>
</tr>
<tr>
<td></td>
<td>• frequent and highly symptomatic episodes in patients with paroxysmal or intermittent AF and/or</td>
</tr>
<tr>
<td></td>
<td>• syncope thought to be due to AF and/or</td>
</tr>
<tr>
<td></td>
<td>• congestive heart failure secondary to AF</td>
</tr>
</tbody>
</table>
References


