Health-Related Quality of Life in Patients With Atrial Fibrillation Treated With Rhythm Control Versus Rate Control

Insights From a Prospective International Registry (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation: RECORD-AF)

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Background—Improving health-related quality of life (HRQoL) is an important treatment goal in the management of patients with atrial fibrillation (AF). Uncertainty exists as to whether patients’ HRQoL differ when treated with medical rhythm control or rate control. We compared HRQoL between patients treated with rhythm control or rate control in a large observational registry of patients with recent-onset AF.

Methods and Results—In the Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation (RECORD-AF), 2439 patients with recent onset (<1 year) AF completed an AF-specific HRQoL questionnaire, the University of Toronto Atrial Fibrillation Severity Scale. HRQoL was assessed by the AF symptom severity score (0–35, with higher scores reflecting more severe AF-related symptoms) at baseline and 1 year. The minimal clinically important difference was defined as a change of ≥3 points. The primary analysis was based on a propensity score-adjusted longitudinal regression analysis which compared the change in AF symptom severity scores between the 2 groups. Over an average follow-up of 1 year, the AF symptom severity scores improved in both groups (rhythm control: −2.82 point [95% confidence interval, −3.22 to −2.41]; rate control: −2.11 point [95% confidence interval, −2.54 to −1.67]; P<0.01 for both groups). The magnitude of improvement was higher in the rhythm control group than the rate control group (unadjusted difference: −0.75 point; 95% confidence interval, −1.31 to −0.19; P=0.01; propensity score-adjusted difference: −0.71 point; 95% confidence interval, −1.31 to −0.11; P=0.02).

Conclusions—In this observational cohort of recent-onset AF patients, treatment with medical rhythm- or rate control over 1 year was associated with an improvement in HRQoL. The magnitude of HRQoL improvement was minimally higher in patients treated with rhythm control than rate control. However, the overall degree of improvement was not large, and its clinical significance was uncertain. (Circ Cardiovasc Qual Outcomes. 2014;7:00-00.)

Key Words: atrial fibrillation ■ quality of life
WHAT IS KNOWN

- In randomized clinical trials comparing medical rhythm control and rate control for patients with atrial fibrillation, no difference in health-related quality of life (HRQoL) had been demonstrated.

WHAT THE STUDY ADDS

- Using an atrial fibrillation-specific questionnaire to assess HRQoL in an international registry of recent onset atrial fibrillation patients, treatment with medical rhythm control or rate control was associated with improvement in HRQoL over an average follow-up period of 1 year.
- Improvement in HRQoL was minimally greater in patients treated with rhythm control than those treated with rate control.
- Overall, the magnitude of improvement was modest, and its clinical significance was uncertain.
- There was a subset of patients who experienced large gains in their HRQoL. Further characterization of this subgroup of high responders may be useful. Otherwise, many patients with atrial fibrillation had little to no change in their HRQoL in spite of cardiologist-directed care.

Therefore, improvement of HRQoL remains highly relevant in the management of patients with AF, as reflected in recent AF guidelines. When the goal of therapy is to improve quality of life, it is unclear whether medical rate control or rhythm control is preferable. Neither strategy was superior to the other in improving patients’ HRQoL in randomized trials. Part of this uncertainty may be related to the use of generic HRQoL instruments which are insensitive to changes in quality of life related to AF symptoms. Also, patients enrolled in randomized trials were highly selected and might not represent those encountered in everyday clinical practice. Finally, confirmation of results from randomized trials in real-world experience is not possible because of a paucity of large-scale, contemporary, real-world AF registry data on HRQoL outcomes.

We performed a prospective evaluation of HRQoL outcomes from a large, contemporary, international observational registry of patients with a recent diagnosis of AF (The Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation: RECORD-AF). We hypothesize that HRQoL will improve over time if patients are treated with rhythm control or rate control. Also, we hypothesize that the magnitude of HRQoL change is greater among patients treated with rhythm control compared with rate control. To address these questions, we evaluated for differences in HRQoL among patients with AF with a disease-specific questionnaire.

Methods

Study Design

The RECORD-AF study was an international, prospective cohort study of patients with recent diagnoses (<1 year) of AF. It included 5604 patients in 532 clinical sites from 21 countries in Europe, North and South America, and Asia. Patient recruitment began in May 2007 and ended in April 2008. The details of study design have been published elsewhere. The study protocol was approved by the research ethics board of the local institutions, and all participants provided written informed consent.

In this article, we report the findings of the prespecified HRQoL substudy of RECORD-AF. The comparison of interest was treatment with medical rhythm control versus rate control, determined by the treating cardiologist at the end of the baseline visit. Medical rhythm control was defined as use of an antiarrhythmic drug (class I, sotalol, or other class III drugs). Patients in the rhythm control group might be cotreated with rate control agents. Medical rate control was defined as use of an atroventricular nodal blocker (nonsotalol β-blocker, calcium channel blocker, and digoxin) without concomitant use of a class I or III antiarrhythmic agent. HRQoL was assessed with a validated, disease-specific AF questionnaire: The University of Toronto Atrial Fibrillation Severity Scale (AFSS, version 3). Specifically, the linear AF symptom severity score component of AF-specific HRQoL. This score is a composite of 7 patient-reported AF-related symptoms. A score of 0 (no symptoms) to 5 (5 worse symptoms) is reported for each parameter, and the AF symptom severity score is the sum of these scores. Scores range from 0 to 35, with higher values reflecting more severe AF-related symptoms.

The primary outcome was the change in AF symptom severity scores between the baseline and final visit (performed at 12±3 months). We chose this score as the primary outcome because it best reflected the HRQoL status of patients with AF, as indicated by their symptoms. Because AF frequency and duration are generally less accurate when subjectively reported by the patient, a score which incorporates these measures may potentially dilute the actual changes of HRQoL in this population. The AF symptom severity score correlates well with other validated, AF-specific HRQoL questionnaires.

Using anchor-based methods, the magnitude of AF-related HRQoL improvement in relation to changes in AF symptom severity scores has been characterized as unimportant (<3 point decrease), small (3–5 point decrease), moderate (6–8 point decrease), large (9–11 point decrease), and very large (>12 point decrease). Accordingly, a change in the AF symptom severity score of ≥3 points is considered to represent the minimal clinically important difference in this analysis.

The AF symptom severity score has been calibrated to a quantitative metric of HRQoL in patients with AF, the Canadian Cardiovascular Society Severity in Atrial Fibrillation Scale (CCS-SAF). The CCS-SAF scale is a clinician-reported assessment of HRQoL for patients with AF. It consists of 5 classes, ranging from class 0 (no symptoms because of AF) to class 4 (severe impact on HRQoL because of AF). On average, an increase of 1 class in the CCS-SAF scale corresponds to a 0.3-point increase in the AF symptom severity score.

Patients were assessed at 3 clinic visits: visit 1 (baseline), visit 2 (at ±2 months, nonmandatory), and visit 3 (at ±2 months). The AFSS questionnaire was administered to patients at the baseline and final visits only. This questionnaire was available in 5 languages and was administered in 8 of the 21 countries which participated in RECORD-AF. The CCS-SAF scale was calibrated to the AF symptom severity score, which was used to assess treatment effects.

Statistical Analysis

Descriptive statistics for continuous variables were expressed as mean±SD. For categorical variables, counts and percentages were expressed. Comparison of baseline characteristics between the rate control and rhythm control groups was performed by the unpaired Student t test for continuous, approximately normally distributed data and the Fisher exact test for categorical variables. Intragroup changes in HRQoL scores from baseline to final follow-up were assessed by the paired Student t test for the rate control and rhythm control groups, respectively. Patients who died during the study or those with missing scores at both the baseline and final visits were excluded. On average, the time between the baseline and final visit was 12±1.8 months. Thus, we assumed a 12-month time span between the initial and final HRQoL measurement.
The primary analysis was the change in HRQoL between rhythm control and rate control over 1 year, after adjustment of baseline differences between the 2 groups. We adjusted for baseline characteristics with a propensity score model which estimated the probability that a patient was treated with rhythm control (versus rate control) at the end of the baseline visit. The selection of covariates for the propensity score model was based on prior knowledge and standards from previous literature. They included age, sex, systolic and diastolic blood pressure, resting heart rate, type of AF, current or previous AF symptoms, use of antiarrhythmic agents, use of vitamin K antagonists, history of heart failure, New York Heart Association class, baseline EuroQol score, residence in the United States, and use of the following medications within the past month: non-sotalol β-blocker, nondihydropyridine calcium channel blocker, digoxin, class III drug, and class I drug. Subjects were stratified into quintiles, with the cutoff value for each strata determined by the estimated propensity score of the combined group. The stratified propensity score was analyzed as a categorical covariate in the longitudinal regression model to assess the effect of treatment group (rhythm control versus rate control), time (baseline versus 12 months), and their interaction (treatment group × time) on the change in AF symptom severity scores.

Sensitivity Analysis

Missing Data
The primary analysis was performed on a nonimputed data set. To account for missing data, imputation was performed to estimate missing values in the overall data set. Twenty-five iterations were performed to impute for the missing data. Results of these analyses were combined to account for the uncertainty of the imputations.

Crossover
A nontrivial proportion of patients crossed over to the other treatment strategy by the end of the study or their crossover status was unknown. Using the same statistical models described above, a subanalysis was performed on the cohort of patients who remained on their original treatment assignment throughout the 1-year study period.

Subgroup Analyses
In the primary analysis, participants’ country of residence was modelled as a binary covariate (United States vs. non–United States). Because 8 countries in RECORD-AF participated in the HRQoL substudy, we performed a sensitivity analysis by using country-specific dummy covariates when modelling the propensity score.

In addition, we compared changes in the AF symptom severity scores between rhythm control and rate control in 2 subgroups which are of interest to clinicians: (1) patients with paroxysmal AF and (2) patients with a history of heart failure.

Statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC). Reported P-values were 2-tailed and tests were conducted at the α=0.05 significance level.

Results
In total, 2646 patients were enrolled in the RECORD-AF HRQoL substudy. Ninety-five (3.6%) patients were excluded because they did not meet inclusion or had exclusion criteria. Of the 2551 eligible patients, 20 (0.8%) patients did not complete any part of the AFSS questionnaire, 63 (2.5%) patients died during the study period, and 29 (1.1%) patients had missing AF symptom severity scores at both the baseline and final visits (Figure 1). These patients were excluded, and the final cohort consisted of 2439 patients. Their baseline characteristics are summarized in Table 1. Compared with those in the rhythm control group, patients in the rate control group were older, more likely to have persistent AF, heart failure, and higher (≥2) congestive heart failure, hypertension, age, diabetes mellitus, prior stroke (CHADS2) scores. The baseline AF symptom severity scores were similar between the 2 groups (rhythm control vs. rate control [mean±SD]: 8.7±7.0 points vs. 8.7±7.0 points; P=0.99).

Missing Data
There were 751 (31%) patients who had missing AF symptom severity scores at either the baseline or final visit (not both). The distribution of missing scores was similar between the rhythm control and rate control groups. In the rhythm control

Figure 1. Study flowchart. AF indicates atrial fibrillation; and AFSS, Atrial Fibrillation Severity Scale.
group, the baseline and follow-up scores were missing in 30 (2.6%) and 331 (28.2%) patients, respectively. In the rate control group, the baseline and follow-up scores were missing in 36 (2.8%) and 354 (27.9%) patients, respectively.

### Within-Group Changes in AF Symptom Severity Scores Over 1 Year

Over an average follow-up period of 1 year, the AF symptom severity score decreased (improved) by 2.69 points (95% confidence interval [CI], −3.10 to −2.28) in the rhythm control group and by 2.08 points (95% CI, −2.50 to −1.66) in the rate control group (\(P<0.01\) in both groups).

### Propensity Score Model

The c-statistic of the propensity score model was 0.85. The median propensity score for patients treated with rhythm control and rate control at the end of the baseline visit was 0.83 and 0.27, respectively. The propensity score distribution of the rhythm control and rate control groups is shown in Figure 2. There was sufficient overlap in the propensity score distributions between the 2 groups to create strata based on quintiles.

### Change in AF Symptom Severity Scores Over 1 Year: Rhythm Control Versus Rate Control

The unadjusted estimate of the change in AF symptom severity scores was higher in the rhythm control group compared with rate control group, by −0.75 point over 1 year (95% CI, −1.31 to −0.19; \(P=0.01\)). After adjustment of baseline differences by propensity score quintiles, patients treated with rhythm control had greater improvement of their AF symptom severity score than those treated with rate control over 1 year (difference between rhythm control versus rate control: −0.71 point, 95% CI, −1.31 to −0.11; \(P=0.02\); Figure 3). Over 1 year, the rhythm control group had a decrease (improvement) of 2.82 points (95% CI, −3.22 to −2.41 points), whereas the rate control group had a decrease of 2.11 points (95% CI, −2.54 to −1.67 points; Figure 3).

### Sensitivity Analyses

#### Missing Data

After missing data were accounted for by multiple imputation, the rhythm control group had greater improvement in the AF symptom severity scores than the rate control group over
1 year (difference between rhythm control versus rate control: −0.61 point; 95% CI, −1.11 to −0.11; \(P=0.02\); Figure 3).

**Crossover**
Of the 2439 patients included in the primary analysis, 558 (22.9%) patients crossed over to the other therapeutic strategy and 252 (10.3%) patients had unknown crossover status at the end of study follow-up. After exclusion of these patients, there were 1629 (66.7%) patients who remained on their originally assigned treatment throughout the study. The baseline characteristics of these cohorts are summarized in Table I in the Data Supplement. In this on-treatment cohort of 1629 patients, the change in AF symptom severity scores was compared between the rhythm control and rate control groups. The unadjusted, propensity score-adjusted, and imputed propensity score-adjusted results are shown in Figure I in the Data Supplement. Patients in the rhythm control group had greater HRQoL improvement than those in the rate control group over 1 year of follow-up (difference between rhythm control versus rate control: −0.84 point, 95% CI, −1.52 to −0.17; \(P=0.02\)).

**Subgroup Analyses**

**Country-Specific Analysis**
The key baseline demographics of patients, divided by their country of residence, are shown in Table II in the Data Supplement. By using country-specific dummy variables to model the propensity score, we observed a similar difference in the change of AF symptom severity scores between the rhythm control and rate control groups over 1 year (difference between rhythm control versus rate control: −0.71 point, 95% CI, −1.31 to −0.12; \(P=0.02\)).

**Paroxysmal AF**
Of the 1255 patients with paroxysmal AF at baseline, 780 (62.2%) patients were treated with rhythm control and 475 (37.8%) were treated with rate control. The rhythm control group had greater improvement of their AF symptom severity scores over 1 year, compared with rate control (rhythm control: −2.51 point [95% CI, −3.03 to −2.00]; rate control: −1.57 point [95% CI, −2.26 to −0.88]; difference between rhythm control versus rate control: −0.94 point [95% CI, −1.81 to −0.08]; \(P=0.03\)).
Discussion

In this prospective, international, observational registry of an inception cohort of AF patients, treatment with either rhythm control or rate control was associated with an improvement in HRQoL over 1 year of follow-up, as measured by the AF symptom severity score. After adjustment for baseline differences, the magnitude of HRQoL improvement was minimally greater among patients treated with rhythm control compared with rate control.

In previous studies, no difference in HRQoL was observed between patients with AF treated with rate control or rhythm control.7–9 Our analyses demonstrated a statistically significant difference in the change of HRQoL over a 1-year period, in favor of rhythm control. There are several possible explanations to account for our findings. First, our study used a disease-specific instrument to assess AF-related HRQoL while most previous studies used generic HRQoL surveys, such as the Medical Outcomes Study 36-item short-form health survey (SF-36).7–9 Generic surveys may lack the sensitivity and specificity required to detect changes of HRQoL in patients with AF.7–9 This could potentially account for the lack of a discernible difference in HRQoL between patients treated with rhythm control versus rate control in those studies. In addition, we chose the AF symptom severity score as the primary outcome of interest, which had been shown to well-correlate with other validated AF-specific HRQoL instruments.15–17 Higher AF symptom severity scores reflect worse symptoms in an incremental and linear fashion.16 Thus, we felt that this was an appropriate metric to evaluate changes of HRQoL in patients with AF over time.

Most previous studies comparing HRQoL in patients treated with rhythm control or rate control were based on subanalyses of randomized clinical trials.7–9 These studies enrolled highly selected patients and might not reflect the usual patient profile encountered in everyday clinical practice. Comparatively, our study enrolled patients in real-world clinical settings in 8 countries from 3 continents. Also, in previous studies, subjects were assigned to medical rhythm control or rate control in a randomized fashion. In RECORD-AF, whether a patient was treated with rhythm control or rate control was based on the judgment of the treating cardiologist, after clinical evaluation. This difference in treatment selection might also explain why our observations differed from those derived from randomized trials.

In spite of cardiologist-directed care in a nonrandomized context and use of an AF-specific questionnaire to assess HRQoL in RECORD-AF, the difference in HRQoL improvement between rhythm control and rate control was numerically small. Several reasons could account for this finding. First, although RECORD-AF included patients with recent (<1 year) diagnoses of AF, a sizeable proportion of them were already treated with medications for rhythm control or rate control before enrollment. This could potentially bias our results toward the null. For instance, patients in the rhythm control group who had been treated with anti-arrhythmic drugs before study enrollment could represent a more stable cohort with less AF-related HRQoL impairment. In addition, the 1-year treatment crossover rate was ≈25% in RECORD-AF, a rate that was higher than randomized trials such as the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial (crossover rate of ≈6% per year) and the Atrial Fibrillation History of Heart Failure

Of the 400 patients with a history of heart failure at baseline, 170 (42.5%) patients were treated with rhythm control and 230 (57.5%) were treated with rate control. There was no difference between the 2 groups in terms of their change in AF symptom severity scores over 1 year (rhythm control: −2.68 point [95% CI, −3.86 to −1.50]; rate control: −2.02 point [95% CI, −3.00 to −1.05]; difference between rhythm control versus rate control: −0.65 point [95% CI, −2.18 to −0.87]; P=0.40).

Distribution of the Magnitude of Change in AF Symptom Severity Scores: Rate Control Versus Rhythm Control

Both the baseline and final AF symptom severity scores were available in 1688 (69.2%) patients from the final cohort. The change in AF symptom severity scores did not improve by ≥3 points over 1 year in either group. The average baseline AF symptom severity score of this group was 3.8±5.7 points. There were 429 (25.4%) patients who had at least moderate improvement of their HRQoL over 1 year, defined as a decrease of ≥6 points of their AF symptom severity score.15 The baseline characteristics of these patients are shown in Table 2. Patients with at least moderate improvement of their HRQoL were younger (66.2±11.5 years versus 68.3±11.6 years; P<0.01) and had worse AF-related symptoms at baseline (15.0±5.8 points versus 6.4±5.9 points; P<0.01) compared with those with less-than-moderate improvement. In both the rhythm control and rate control groups, the AF symptom severity scores improved over 1 year (rhythm control: −10.78 point [95% CI, −11.36 to −10.19]; rate control: −10.14 point [95% CI, −10.79 to −9.50]). The change in AF symptom severity scores was similar between the 2 groups (difference between rhythm control versus rate control: −0.63 point [95% CI, −1.50 to 0.24]; P=0.16).

Figure 4. Distribution of the magnitude of change in atrial fibrillation (AF) symptom severity scores. The change in AF symptom severity scores was calculated from 1688 patients (69.2%) in the final cohort of 2439 patients. In these patients, both the baseline and final AF symptom severity scores were available for analysis. Lower (more negative) values denote greater improvement of the AF symptom severity score.

Distribution of the Magnitude of Change in AFSS

In this prospective, international, observational registry of an inception cohort of AF patients, treatment with either rhythm control or rate control was associated with an improvement in HRQoL over 1 year of follow-up, as measured by the AF symptom severity score. After adjustment for baseline differences, the magnitude of HRQoL improvement was minimally greater among patients treated with rhythm control compared with rate control.

In previous studies, no difference in HRQoL was observed between patients with AF treated with rate control or rhythm control.7–9 Our analyses demonstrated a statistically significant difference in the change of HRQoL over a 1-year period, in favor of rhythm control. There are several possible explanations to account for our findings. First, our study used a disease-specific instrument to assess AF-related HRQoL while most previous studies used generic HRQoL surveys, such as the Medical Outcomes Study 36-item short-form health survey (SF-36).7–9 Generic surveys may lack the sensitivity and specificity required to detect changes of HRQoL in patients with AF.7–9 This could potentially account for the lack of a discernible difference in HRQoL between patients treated with rhythm control versus rate control in those studies. In addition, we chose the AF symptom severity score as the primary outcome of interest, which had been shown to well-correlate with other validated AF-specific HRQoL instruments.15–17 Higher AF symptom severity scores reflect worse symptoms in an incremental and linear fashion.16 Thus, we felt that this was an appropriate metric to evaluate changes of HRQoL in patients with AF over time.

Most previous studies comparing HRQoL in patients treated with rhythm control or rate control were based on subanalyses of randomized clinical trials.7–9 These studies enrolled highly selected patients and might not reflect the usual patient profile encountered in everyday clinical practice. Comparatively, our study enrolled patients in real-world clinical settings in 8 countries from 3 continents. Also, in previous studies, subjects were assigned to medical rhythm control or rate control in a randomized fashion. In RECORD-AF, whether a patient was treated with rhythm control or rate control was based on the judgment of the treating cardiologist, after clinical evaluation. This difference in treatment selection might also explain why our observations differed from those derived from randomized trials.

In spite of cardiologist-directed care in a nonrandomized context and use of an AF-specific questionnaire to assess HRQoL in RECORD-AF, the difference in HRQoL improvement between rhythm control and rate control was numerically small. Several reasons could account for this finding. First, although RECORD-AF included patients with recent (<1 year) diagnoses of AF, a sizeable proportion of them were already treated with medications for rhythm control or rate control before enrollment. This could potentially bias our results toward the null. For instance, patients in the rhythm control group who had been treated with anti-arrhythmic drugs before study enrollment could represent a more stable cohort with less AF-related HRQoL impairment. In addition, the 1-year treatment crossover rate was ≈25% in RECORD-AF, a rate that was higher than randomized trials such as the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial (crossover rate of ≈6% per year) and the Atrial Fibrillation History of Heart Failure

Of the 400 patients with a history of heart failure at baseline, 170 (42.5%) patients were treated with rhythm control and 230 (57.5%) were treated with rate control. There was no difference between the 2 groups in terms of their change in AF symptom severity scores over 1 year (rhythm control: −2.68 point [95% CI, −3.86 to −1.50]; rate control: −2.02 point [95% CI, −3.00 to −1.05]; difference between rhythm control versus rate control: −0.65 point [95% CI, −2.18 to −0.87]; P=0.40).

Distribution of the Magnitude of Change in AF Symptom Severity Scores: Rate Control Versus Rhythm Control

Both the baseline and final AF symptom severity scores were available in 1688 (69.2%) patients from the final cohort. The distribution of the changes in scores of the rhythm control (n=877) and rate control (n=811) groups is shown in Figure 4. In this cohort, there were 1075 (63.9%) patients whose AF symptom severity scores did not improve by ≥3 points over 1 year. The average baseline AF symptom severity score of this group was 3.8±5.7 points. There were 429 (25.4%) patients who had at least moderate improvement of their HRQoL over 1 year, defined as a decrease of ≥6 points of their AF symptom severity score.15 The baseline characteristics of these patients are shown in Table 2. Patients with at least moderate improvement of their HRQoL were younger (66.2±11.5 years versus 68.3±11.6 years; P<0.01) and had worse AF-related symptoms at baseline (15.0±5.8 points versus 6.4±5.9 points; P<0.01) compared with those with less-than-moderate improvement. In both the rhythm control and rate control groups, the AF symptom severity scores improved over 1 year (rhythm control: −10.78 point [95% CI, −11.36 to −10.19]; rate control: −10.14 point [95% CI, −10.79 to −9.50]). The change in AF symptom severity scores was similar between the 2 groups (difference between rhythm control versus rate control: −0.63 point [95% CI, −1.50 to 0.24]; P=0.16).

Figure 4. Distribution of the magnitude of change in atrial fibrillation (AF) symptom severity scores. The change in AF symptom severity scores was calculated from 1688 patients (69.2%) in the final cohort of 2439 patients. In these patients, both the baseline and final AF symptom severity scores were available for analysis. Lower (more negative) values denote greater improvement of the AF symptom severity score.
and Congestive Heart Failure (AF-CHF) trial (crossover rate of \(\approx 10\%\) per year).\(^3,4\) A high rate of crossover could have diluted the HRQoL difference between patients treated with rhythm control or rate control in this study. When our analysis was restricted to patients who stayed on their original treatment over 1 year, the numeric difference in HRQoL between the 2 groups was slightly greater than the primary analysis which included patients who crossed over. Finally and most importantly, we speculate that the actual 1-year difference in HRQoL between rhythm control and rate control is small. This could explain why previous studies did not demonstrate a difference in HRQoL. The larger sample size of our analysis likely provided more statistical power to detect relatively small effect sizes, \(\approx 1\)-point difference between the 2 groups.

Although there was a statistically significant improvement in HRQoL in favor of rhythm control, the key question is whether this difference is clinically meaningful. Our results suggest that the magnitude of HRQoL improvement in patients treated with rhythm control might be clinically relevant. In this group, the AF symptom severity score improved by \(\approx 3\) points \((-2.82\text{ points}, 95\%\ Cl. -3.22\text{ to }-2.41\) over 1 year, reflecting an estimated improvement of 1 CCS-SAF class.\(^8\) An improvement of this magnitude had been shown to be clinically relevant, as higher (worse) SAF class was associated with more emergency room visits and hospitalizations, reflecting greater consumption of healthcare resources.\(^16\) However, this possible signal of benefit was not observed in the rate control group, as the magnitude of HRQoL improvement did not cross our predefined clinically relevant threshold of \(-3.0\) points (rate control: \(-2.11\) point; \(95\%\ Cl., -2.54\text{ to }-1.67\)).

Although both treatment strategies were associated with a numeric improvement in AF symptom severity scores over time, a sizeable proportion of patients did not experience clinically meaningful improvement of their HRQoL, even with cardiologist-directed care. In the subgroup of 1688 patients with available baseline and final follow-up AF symptom severity scores, 1075 \((63.7\%\)) of patients did not experience a clinically meaningful improvement of their scores. These patients had relatively low

| Table 2. Baseline Demographics of Patients With \(\geq 6\) Point Decrease (Moderate Improvement) of the AF Symptom Severity Score |
|---|---|---|
| \(\geq 6\) Point Decrease (n=429) | \(<6\) Point Decrease (n=1259) | \(P\) Value |
| Rhythm control selected at the end of baseline visit, n (%) | 231 (53.9) | 646 (51.3) | 0.37 |
| Male, n (%) | 230 (53.6) | 742 (58.9) | 0.05 |
| Age (mean±SD) | \(66.2\pm11.5\) | \(68.3\pm11.6\) | <0.01 |
| Systolic BP at baseline, mm Hg (mean±SD) | \(130.9\pm19.0\) | \(133.1\pm19.3\) | 0.04 |
| Resting heart rate at baseline, bpm (mean±SD) | \(80.3\pm22.2\) | \(75.5\pm19.3\) | <0.01 |
| Paroxysmal AF, n (%) | 212 (49.4) | 674 (53.5) | 0.15 |
| Persistent AF, n (%) | 188 (43.8) | 514 (40.8) | 0.43 |
| CHADS\(\text{S}_{2}\), score \(\geq 2\), n (%) | 168 (39.3) | 522 (41.8) | 0.39 |
| Antithrombotic at baseline, n (%) | 382 (89.0) | 1083 (86.0) | 0.12 |
| Vitamin K antagonist use at baseline, n (%) | 271 (63.2) | 768 (61.0) | 0.46 |
| History of heart failure, n (%) | 78 (18.2) | 199 (15.8) | 0.26 |
| Heart failure symptoms, n (%) | \(\leq 0.01\) |
| None | 351 (81.8) | 1059 (84.3) |
| NYHA I or II | 60 (14.0) | 177 (14.1) |
| NYHA III or IV | 18 (4.2) | 20 (1.6) |
| Previous or current history of AF symptoms at baseline, n (%) | 361 (84.2) | 947 (75.2) | 1.0 |
| Smoking status, n (%) | \(0.32\) |
| Never | 208 (51.6) | 668 (53.9) |
| Current | 35 (8.7) | 98 (8.2) |
| Former | 160 (39.7) | 429 (35.9) |
| Use of medications within the past month, n (%) | \(0.01\) |
| Class I drug | 43 (10.3) | 138 (11.4) | 0.65 |
| \(\beta\)-Blockers (except sotalol) | 251 (60.3) | 762 (62.7) | 0.41 |
| Class II drug | 133 (32.0) | 343 (28.2) | 0.15 |
| Rate-lowering calcium channel blocker | 53 (12.7) | 198 (16.3) | 0.08 |
| Digoxin | 110 (26.4) | 247 (20.3) | 0.01 |
| Baseline AF symptom severity score (mean±SD) | 15.0±5.8 | 6.4±5.9 | <0.01 |

Results were derived from the cohort of 1688 patients \((69.2\%\)) in whom both the baseline and final AF symptom severity scores were available for analysis. Higher AF symptom severity scores indicate more severe AF-related symptoms. AF indicates atrial fibrillation; AFSS, Atrial Fibrillation Severity Scale; BP, blood pressure; HRQoL, health-related quality of life; and NYHA, New York Heart Association.
baseline AF symptom severity scores (5.8±5.7 points), suggesting that their HRQoL was not significantly impaired by AF at the time of enrollment. Therefore, therapies intended to improve AF-related symptoms (rhythm control or rate control) would not be expected to produce large gains in these patients’ HRQoL. In the HRQoL substudy of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, no difference in HRQoL was observed between subjects treated with rhythm control and rate control. Notably, the baseline SF-36 summary and component scores of subjects in that study were similar to age-adjusted mean scores of US patients without AF.7 The summary of our study findings and others provide a plausible explanation for why little to no gain in HRQoL was observed in published studies to date.

Corollary findings were observed in the 429 (25.4%) patients who had at least moderate improvement (26 point decrease) in their AF symptoms severity scores, which largely drove the observed improvement in HRQoL of the overall cohort. Within this subgroup, patients had high baseline AF symptom severity scores (15.0±5.8 points), reflecting significant impairment in their AF-related HRQoL. These patients had the greatest magnitude of HRQoL improvement, by ≈10 points over 1 year. Our findings suggest that the magnitude of AF-related HRQoL gains is dependent on patients’ baseline AF symptom burden. If so, this will highlight a potential role of disease-specific HRQoL questionnaires such as AFSS to identify patients whose HRQoL are most severely affected by AF. Worse HRQoL in AF patients had been associated with greater rates of hospitalization and increased mortality.8-10 As such, identification of these patients may allow clinicians to concentrate their treatment efforts and resources to procure the largest gains in HRQoL. This concept is speculative and requires prospective confirmation.

Limitations
The results of this study were derived from a prospective observational registry of patients with AF. As such, it is subject to selection bias and confounding because of its nonrandomized design. To account for this, we performed propensity score modeling to adjust for differences in baseline characteristics between the 2 groups. There was a nontrivial proportion of patients with missing baseline or final AF symptom severity scores (31%). To account for reporting bias because of missing data, we performed multiple imputation and noted similar results between the imputed and nonimputed analyses. Finally, it should also be noted that our statistical model was relatively insensitive to handle patients who crossed over to the other treatment strategy. However, our results are similar when these patients are excluded in the sensitivity analysis.

Conclusions
In this prospective cohort of recent-onset AF patients, physician-directed treatment with either rhythm control or rate control over an average follow-up period of 1 year was associated with improvement in HRQoL. Although the overall difference was relatively modest, there was a subset of patients who experienced large gains in HRQoL. After adjusting for baseline factors, the degree of improvement in HRQoL was minimally higher in patients treated with rhythm control compared with rate control.

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Health-Related Quality of Life in Patients With Atrial Fibrillation Treated With Rhythm Control Versus Rate Control: Insights From a Prospective International Registry (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation: RECORD-AF)


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