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Rhythm Control Versus Rate Control and Clinical Outcomes in Patients With Atrial Fibrillation

Results From the ORBIT-AF Registry

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ABSTRACT

OBJECTIVES The study sought to evaluate clinical outcomes in clinical practice with rhythm control versus rate control strategy for management of atrial fibrillation (AF).

BACKGROUND Randomized trials have not demonstrated significant differences in stroke, heart failure, or mortality between rhythm and rate control strategies. The comparative outcomes in contemporary clinical practice are not well described.

METHODS Patients managed with a rhythm control strategy targeting maintenance of sinus rhythm were retrospectively compared with a strategy of rate control alone in a AF registry across various U.S. practice settings. Unadjusted and adjusted (inverse-propensity weighted) outcomes were estimated.

RESULTS The overall study population (N = 6,988) had a median of 74 (65 to 81) years of age, 56% were males, 77% had first detected or paroxysmal AF, and 68% had $CHADS_2$ score ≥2. In unadjusted analyses, rhythm control was associated with lower all-cause death, cardiovascular death, first stroke/non-central nervous system systemic embolization/transient ischemic attack, or first major bleeding event (all $p < 0.05$); no difference in new onset heart failure ($p = 0.28$); and more frequent cardiovascular hospitalizations ($p = 0.0006$). There was no difference in the incidence of pacemaker, defibrillator, or cardiac resynchronization device implantations ($p = 0.99$). In adjusted analyses, there were no statistical differences in clinical outcomes between rhythm control and rate control treated patients (all $p > 0.05$); however, rhythm control was associated with more cardiovascular hospitalizations (hazard ratio: 1.24; 95% confidence interval: 1.10 to 1.39; $p = 0.0003$).

CONCLUSIONS Among patients with AF, rhythm control was not superior to rate control strategy for outcomes of stroke, heart failure, or mortality, but was associated with more cardiovascular hospitalizations.
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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

CNS = central nervous system

HR = hazard ratio

TIA = transient ischemic attack

Many patients with atrial fibrillation (AF) warrant maintenance of sinus rhythm to control symptoms and improve the quality of life (1-3). Randomized clinical trials including the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) (4), RACE (Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation Study) (5), and the AF-CHF (Atrial Fibrillation and Congestive Heart Failure) trials (6) failed to demonstrate that rhythm control improved cardiovascular outcomes or mortality relative to rate control (7). Further, rhythm control was associated with higher hospitalizations (4-6). However, post hoc nonrandomized analysis of the AFFIRM trial suggested that patients who successfully maintained sinus rhythm had lower mortality than those who failed to maintain sinus rhythm (8). It is unclear if adverse effects of antiarrhythmic drug therapy mitigated benefits of maintaining sinus rhythm, or if sinus rhythm was just a correlate of other confounding predictors of survival not captured in the analysis.

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Contemporary observational data on hospitalized patients with AF suggest that rhythm control may have a marginal mortality benefit over rate control during long-term follow-up (9). Overall, in the U.S. clinical practice, one-third of AF patients are on a rhythm control strategy (10). Both international and U.S. data suggest that there are significant differences in the population of patients selected for rhythm control versus rate control (10-13). Results from the aforementioned trials have presumably impacted clinical practice and approach towards use of antiarrhythmic drugs, and we sought to evaluate the contemporary clinical practice of rhythm control versus rate control. We utilized data from the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) registry to evaluate comparative outcomes for rhythm control versus rate control in a broad practice-based cohort of patients with AF.

METHODS

The ORBIT-AF registry is a registry of U.S. patients with AF who are treated by internists, cardiologists or electrophysiologists. The ORBIT-AF registry enrolled patients from a nationally representative sample of 176 U.S. practices between June 29, 2010 and August 9, 2011. The rationale and design of the registry have been previously described (14). In brief, patients were eligible if they were ≥18 years of age with electrocardiographic (ECG) evidence of AF and were able to provide informed consent and follow-up. Exclusion criteria included <6 months of life expectancy or AF due to a reversible cause such as pulmonary embolism. Data were collected by inputting data from the clinical chart into a web-based case report form and included data on age, sex, race/ethnicity, insurance status, education level, cardiovascular risk factors, date of diagnosis, type of AF (first detected, paroxysmal or persistent), pharmacologic treatment strategy (rhythm control vs. rate control), AF ablation history, cardioversion history, vital signs, laboratory data, ECG findings, transthoracic and transesophageal echocardiographic findings, antithrombotic therapy and monitoring (international normalized ratios), concomitant medications, insurance status and provider information, comorbidities, and outcomes. Follow-up data were collected every 6 months and follow-up duration was 24 to 36 months. The Duke Institutional Review Board approved the ORBIT-AF registry, and all participating sites have obtained institutional review board approval pursuant to local requirements. All subjects provided written, informed consent.

STUDY POPULATION. For the purpose of this analysis, the cohort included patients with first detected/new onset, or paroxysmal, or persistent AF, who had at least 1 follow-up. Patients were classified based on the AF treatment strategy selected for management by the treating physician, rhythm control versus rate control, captured through the mutually exclusive check box in the case-report form. The goal of rhythm control is to attempt maintenance of sinus rhythm using any therapeutic plan that could include cardioversions, antiarrhythmic drugs, and/or atrial ablation. From the ORBIT-AF registry population of 10,135, patients were excluded if information on treatment strategy was missing (n = 24, 0.002%), they had permanent AF (n = 2,827, 27.9%), or if they did not have any follow-up (n = 296, 2.9%) (**Figure 1**).

adjudications committee for GlaxoSmithKline. Dr. Steinberg has served as a consultant to Bristol-Myers Squibb. Dr. Peterson has served as a consultant for Janssen, AstraZeneca, Bayer, Merck, and Boehringer Ingelheim. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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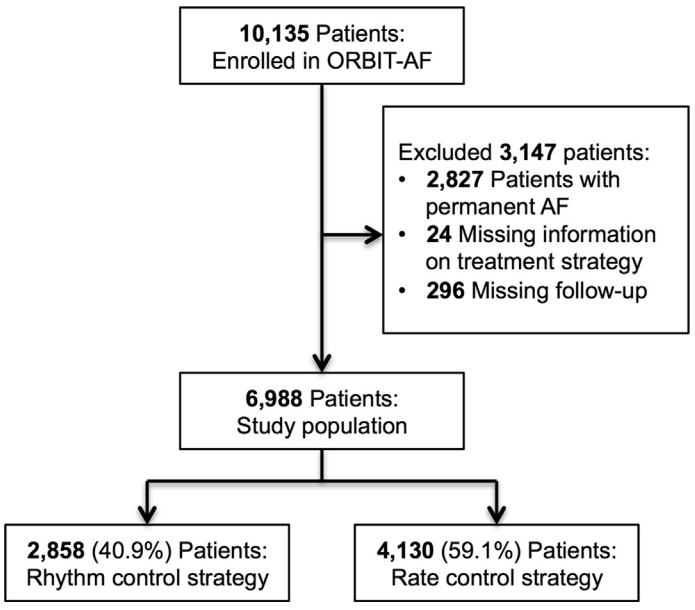
STUDY OUTCOMES. We assessed the following outcomes at follow-up: 1) all-cause death; 2) cardiovascular death; 3) first cardiovascular hospitalization; 4) cardiovascular hospitalization or death; 5) first stroke, non-central nervous system (CNS) systemic embolism, or transient ischemic attack (TIA); 6) the composite of death, stroke, non-CNS embolism, and TIA; 7) new onset heart failure; and 8) first major bleeding (15).

STATISTICAL ANALYSES. Statistical analyses were performed using SAS software (version 9.3, SAS Institute, Cary, North Carolina), and 2-tailed p value of 0.05 was considered the significance threshold for all statistical tests. Baseline characteristics are presented as percentages for categorical variables, and median (interquartile range) for continuous variables, stratified by AF management strategy. Characteristics are compared using chi-square tests for categorical variables and the Wilcoxon rank sum test for continuous variables. The association of AF management strategy with outcomes of interest was assessed using Cox proportional hazards models with a robust sandwich covariance estimate in order to account for the covariance within participating sites. First, unadjusted models were used to analyze the associations of AF management strategy with each outcome. Second, the model predicting each outcome was adjusted for the propensity to receive either treatment by inverse propensity weighting. The propensity score predicting AF management strategy was derived using logistic regressions using imputed data. The propensity score was adjusted for all independent predictors of AF management strategy identified in our prior publication describing the clinical practice of rhythm versus rate control (10) and all additional independent predictors using backward selection, as associated with any of the outcomes of interest for this paper ($p < 0.05$ required to stay in model). Continuous covariates in the propensity model were checked for linearity (no nonlinear relationships were detected). All subjects with a propensity below the 1 percentile were excluded from the adjusted models. The hazard ratio (HR) of rhythm control subjects relative to rate control subjects is reported for all models, along with the corresponding 95% confidence interval (CI) and p value.

Incidence rates per 100-subject years are presented for incident cardioversions, implanted devices, and interventional therapy for AF. The HR and p value from unadjusted Cox proportional hazards models with a robust sandwich covariance estimate are presented.

Age, AF type (first detected/new onset vs. recurrent paroxysmal versus recurrent persistent), and left ventricular systolic function were assessed as potential effect modifiers. For these analyses, interaction terms are added to the propensity model. The inverse propensity weighted model was repeated once for each potential modifier. An interaction term for the modifier and AF management strategy was added into the models. Any significant interaction ($p \leq 0.05$) was followed up with additional models stratified by the effect modifier. In order to avoid any bias associated with prior failed rhythm control therapy, we performed sensitivity analyses excluding any rate control patients with a prior history of antiarrhythmic drug therapy (n = 1,385).

FIGURE 1 Flow Diagram Showing Exclusions and the Treatment Strategy Assignments for the Study Population



AF = atrial fibrillation; ORBIT-AF = Outcomes Registry for Better Informed Treatment of Atrial Fibrillation.

RESULTS

BASELINE CHARACTERISTICS. Among 6,988 patients with first detected/new onset or recurrent paroxysmal AF, 2,858 (40.9%) were treated with rhythm control and 4,130 (59.1%) with a rate control strategy. The baseline characteristics of the cohort according to treatment strategy are shown in Table 1. Patients in the rhythm control group were younger than the rate control group (71 [63 to 79] years vs. 75 [67 to 82] years) and had a marginal but statistically lower prevalence of hypertension, diabetes, chronic kidney

TABLE 1 Baseline Characteristics by AF Management Strategy

	Level	Overall (N = 6,988)	Rhythm Control (n = 2,858)	Rate Control (n = 4,130)	p Value*
Demographics					
Age, yrs†		74 (65–81)	71 (63–79)	75 (67–82)	**<0.0001**
Race	White	90.13	91.99	88.84	**<0.0001**
	Black or African American	4.78	4.13	5.23	
	Hispanic	3.56	2.38	4.38	
	Other	1.37	1.29	1.43	
Sex	Male	56.27	56.86	55.86	0.4082
Medical history					
Smoking	Nonsmoker	52.99	51.64	53.92	0.1764
	Recent or former smoker	41.17	42.30	40.39	
	Current smoker	5.82	6.02	5.69	
Hyperlipidemia	Yes	71.29	70.71	71.69	0.3728
Hypertension	Yes	81.84	79.29	83.61	**<0.0001**
Diabetes	Yes	28.32	26.14	29.83	**0.0008**
Chronic kidney disease (MDRD criteria)	Yes	33.16	31.53	34.29	**0.0069**
Peripheral vascular disease	Yes	12.32	11.13	13.15	**0.0115**
History of stroke/transient ischemic attack	Yes	14.18	13.09	14.94	**0.0290**
History of coronary artery disease	Yes	35.22	33.48	36.42	**0.0117**
Significant valvular disease	Yes	22.34	20.12	23.87	**0.0002**
Obstructive sleep apnea	Yes	18.30	19.80	17.26	**0.0069**
Chronic obstructive pulmonary disease	Yes	15.33	14.35	16.00	0.0584
Liver disease	Yes	1.77	1.96	1.65	0.3300
Anemia	Yes	17.07	15.64	18.06	**0.0081**
Cancer	Yes	22.50	21.20	23.39	**0.0314**
Cognitive impairment/dementia	Yes	2.80	2.10	3.29	**0.0030**
Frailty	Yes	5.18	3.25	6.51	**<0.0001**
Implanted device					
Implanted device	Overall	25.89	23.90	27.26	**0.0016**
	Pacemaker	17.57	15.50	19.01	**0.0002**
	Implanted cardioverter-defibrillator	4.67	4.93	4.48	0.3745
	Cardiac resynchronization therapy-pacemaker	0.69	0.56	0.77	0.2853
	Cardiac resynchronization therapy-defibrillator	3.35	3.32	3.37	0.9264
Congestive heart failure					
Etiology of cardiomyopathy	Ischemic	11.95	9.94	13.34	**<0.0001**
	Nonischemic	17.26	16.13	18.04	
Functional status	No congestive heart failure	70.62	73.83	68.40	**<0.0001**
	NYHA functional class I	9.89	8.64	10.75	
	NYHA functional class II	13.01	12.00	13.70	
	NYHA functional class III/IV	6.33	5.39	6.97	
Heart failure hospitalizations in past year	Yes	5.78	6.23	5.47	0.1831
Left ventricular ejection fraction type†	Missing	10.02	8.71	10.92	**0.0150**
	Normal (≥50%)	72.05	74.53	70.34	
	Mild dysfunction (>40% to <50%)	5.37	4.72	5.81	
	Moderate dysfunction (≥30% to 40%)	8.51	7.91	8.93	
	Severe dysfunction (<30%)	4.05	4.13	4.00	

Continued on the next page

TABLE 1 Continued

	Level	Overall (N = 6,988)	Rhythm Control (n = 2,858)	Rate Control (n = 4,130)	p Value*
Vital signs and AF status					
Body mass index, kg/m^2†		29.09 (25.35–33.98)	29.53 (25.75–34.51)	28.78 (25.08–33.74)	**<0.0001**
Heart rate, beats/min†		70 (62–78)	68 (60–76)	71 (64–80)	**<0.0001**
Type of AF	First detected/new onset	6.24	5.56	6.71	**<0.0001**
	Paroxysmal atrial fibrillation	70.46	76.42	66.34	
	Persistent atrial fibrillation	23.30	18.02	26.95	
European Heart Rhythm Association Score	No symptoms	34.89	30.16	38.16	**<0.0001**
	Mild (normal daily activity not affected)	46.41	47.97	45.33	
	Severe (normal daily activity affected)	16.23	18.82	14.43	
	Disabling (normal daily activity discontinued)	2.19	2.69	1.84	
Catheter ablation of AF	Yes	6.67	10.29	4.16	**<0.0001**
Oral anticoagulant therapy (warfarin or dabigatran)	Yes	72.21	68.37	74.87	**<0.0001**
$CHADS_2$ risk score†	0	7.68	9.90	6.15	**<0.0001**
	1	23.88	27.50	21.38	
	≥2	68.43	62.60	72.47	
ATRIA score	0–3	81.37	83.45	79.93	**<0.0001**
	4	6.01	6.02	6.00	
	5 or more	12.62	10.53	14.07	

Values are median (interquartile range) or percent unless otherwise indicated. All tests treat the column variable as nominal. *The p values do not correspond to the table exactly as it is presented here. More appropriately, p values were calculated by comparing only nonmissing row values; p values are based on Pearson chi-square tests for all categorical row variables. †The p values are based on chi-square rank based group means score statistics for all continuous/ordinal row variables. This is equivalent to Wilcoxon tests. **Bolded** values reflect 2-tailed $p < 0.05$.

AF = atrial fibrillation; MDRD = Modification of Diet in Renal Disease formula; NYHA = New York Heart Association.

disease, vascular disease, valvular heart disease, anemia, cancer, dementia, and frailty. CHA_2DS_2-VASc risk score was ≤1 among 8.4% patients in the rhythm control group versus 14.4% patients on rate control ($p < 0.0001$). The rhythm control group was less likely to have an implanted pacemaker and less likely to have a diagnosis of cardiomyopathy (ischemic or non-ischemic). Furthermore, the rhythm control group had a higher proportion of paroxysmal AF, higher European Heart Rhythm Association symptom class, were more likely to have had prior catheter ablation of AF, but less likely to be on oral anticoagulation therapy (Table 1). Among the rhythm control group, 23.6% of patients were on amiodarone and 49% were on other antiarrhythmic drugs.

CARDIOVASCULAR OUTCOMES. The median (interquartile range) follow-up was 2.3 (1.8 to 2.9) years. The proportional hazards assumption was statistically tested and satisfied. In unadjusted analyses, the rhythm control patients as compared to the rate control group had lower all-cause death ($p < 0.0001$), lower cardiovascular death ($p = 0.015$), fewer first stroke/non-CNS systemic embolization/TIA ($p = 0.028$), and fewer first major bleeding events ($p = 0.0039$). There was no statistical difference in new onset congestive heart failure ($p = 0.28$). Rhythm control was however associated with a higher rate of a first cardiovascular hospitalization ($p = 0.0006$) (Table 2). In the adjusted analyses, there were no statistical differences in clinical outcomes between the 2 groups, except for a higher risk of a first cardiovascular hospitalization (HR: 1.24; 95% CI: 1.10 to 1.39; $p = 0.0003$) with rhythm control. The adjusted relative hazard of the composite endpoint of death, stroke, non-CNS embolism, and TIA was 0.90 (95% CI: 0.77 to 1.06; $p = 0.20$) (Table 2).

As shown in Table 3, the rhythm control strategy was associated with a higher rate of pharmacologic and electrical cardioversions, transesophageal echocardiography, and catheter ablation of AF (all $p < 0.0001$). The 2 groups had similar rates of pacemaker, cardiac resynchronization therapy or implantable cardioverter-defibrillator insertion.

SENSITIVITY ANALYSES. There was no evidence of modification of the association between AF management strategy and the adjusted clinical outcomes by age or left ventricular systolic function. However, there was evidence of an interaction between AF type (first detected/new onset vs. recurrent paroxysmal versus recurrent persistent AF) and AF management

TABLE 2 Incidence of Outcomes by AF Management Strategy and Associations Between AF Management Strategy and Outcomes (N = 6,988)

Outcome	Rhythm Control		Rate Control		Unadjusted Results		Adjusted Results*	
	Events	Rate†	Events	Rate†	HR‡ (95% CI)	p Value	HR‡ (95% CI)	p Value
All-cause death	247	3.81	515	5.79	0.65 (0.55–0.77)	**<0.0001**	0.87 (0.72–1.04)	0.1161
CV death	101	1.56	197	2.23	0.69 (0.52–0.93)	**0.0149**	0.96 (0.69–1.32)	0.7947
First CV hospitalization	992	19.41	1,175	15.92	1.22 (1.09–1.37)	**0.0006**	1.24 (1.10–1.39)	**0.0003**
CV hospitalization or death	1,121	21.93	1,477	20.01	1.10 (0.99–1.21)	0.0664	1.16 (1.05–1.29)	**0.0032**
First stroke, non-CNS embolism, or TIA	73	1.14	135	1.54	0.73 (0.56–0.97)	**0.0282**	0.87 (0.66–1.16)	0.3452
Composite of death, stroke, non-CNS embolism, and TIA	308	4.80	602	6.86	0.69 (0.60–0.80)	**<0.0001**	0.90 (0.77–1.06)	0.2032
New-onset congestive heart failure§	54	1.13	84	1.38	0.83 (0.59–1.17)	0.2796	0.92 (0.63–1.34)	0.6742
First major bleeding event	185	2.94	323	3.77	0.78 (0.66–0.92)	**0.0039**	0.91 (0.76–1.08)	0.2699

*Adjusted results are from inverse propensity weighted models. †Incidence rate presents the number of events per 100 subject-years follow-up. ‡Hazard ratio (HR) is for rhythm control relative to rate control. §Congestive heart failure at baseline is excluded. **Bolded** values reflect 2-tailed $p < 0.05$.

AF = atrial fibrillation; CI = confidence interval; CNS = central nervous system; CV = cardiovascular; MDRD = Modification of Diet in Renal Disease formula; TIA = transient ischemic attack.

strategy with respect to first cardiovascular hospitalization (p = 0.012), with a trend toward a higher adjusted risk of cardiovascular hospitalizations with rhythm control strategy in patients with recurrent persistent AF (HR: 1.49; 95% CI: 1.20 to 1.84) versus recurrent paroxysmal AF (HR: 1.17; 95% CI: 1.03 to 1.34) (Table 4).

All of our results remained qualitatively similar when we excluded all rate control patients with a prior history of antiarrhythmic drug therapy. Similarly, there was no appreciable change in the results with inclusion of baseline oral anticoagulation status as an additional covariate for the propensity scores used in the adjusted models.

TABLE 3 Incidence Rate of Interventions During Follow-Up Period by AF Management Strategy (N = 6,988)

Outcome	Rhythm Control		Rate Control			
	Events	Rate*	Events	Rate*	HR† (95% CI)	p Value
Cardioversion						
Pharmacologic	98	1.55	60	0.68	2.29 (1.56–3.37)	**<0.0001**
DC cardioversion	427	7.33	263	3.11	2.37 (1.96–2.86)	**<0.0001**
TEE	139	2.21	97	1.11	2.01 (1.48–2.73)	**<0.0001**
Implanted device						
Pacemaker	114	1.80	153	1.77	1.03 (0.80–1.33)	0.8025
ICD	37	0.57	48	0.54	1.06 (0.67–1.70)	0.7921
BiV (CRT-P)	15	0.23	19	0.21	1.09 (0.59–2.02)	0.7881
BiV-ICD (CRT-D)	41	0.64	59	0.67	0.96 (0.61–1.50)	0.8612
Overall	198	3.19	274	3.22	1.00 (0.81–1.23)	0.9916
Interventional therapy						
Catheter ablation of AF	246	4.03	105	1.20	3.37 (2.60–4.36)	**<0.0001**
Atrial flutter ablation	52	0.81	37	0.42	1.98 (1.25–3.13)	**0.0035**
Surgical Maze/hybrid Maze	33	0.51	20	0.23	2.30 (1.32–3.99)	**0.0032**
AV node/HIS bundle ablation	44	0.68	34	0.38	1.80 (1.11–2.92)	**0.0173**

*Incidence rate presents the number of events per 100 subject-years follow-up. †Hazard ratio (HR) and p value are from Cox proportional hazards model with robust sandwich covariance estimate. **Bolded** values reflect 2-tailed $p < 0.05$.

AF = atrial fibrillation; AV = atrioventricular; BiV = biventricular pacemaker; CI = confidence interval; CRT = cardiac resynchronization therapy; D = defibrillator; DC = direct current; ICD = implantable cardioverter-defibrillator; P = pacemaker; TEE = transesophageal echocardiogram.

DISCUSSION

In this analysis of AF management in contemporary clinical practice, we did not find an independent difference in mortality, heart failure, or systemic embolic events with rhythm or rate control strategies. However, we did observe a higher rate of cardiovascular hospitalization in those treated with rhythm control. These observational findings from community practices largely reflect the findings from older randomized controlled comparisons of rhythm and rate control therapies.

COMMUNITY PERSPECTIVE ON MANAGEMENT OF AF. A Quebec population database study showed no differences in mortality over initial 4 years of follow-up for newly diagnosed AF among hospitalized patients initially prescribed rhythm control versus rate control drugs (9). This analysis was limited to ≥66-year-old hospitalized patients with AF, implied rhythm control based on drug prescriptions within 1 week of hospital discharge, and was affected by changes in treatment practice during follow-up due to publication of the AFFIRM trial (4). In contrast, our analysis has a wider applicability to the larger population of AF patients managed outside the hospital, and directly assesses the intended strategy of rhythm versus rate control for management of AF. Another registry from 532 sites in 21 countries in Europe, America, and Asia, the RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation) registry, followed 3,076 patients on rhythm control and 2,528 patients on rate control (11). The therapeutic target of

TABLE 4 Adjusted Association Between First Cardiovascular Hospitalization and AF Management Strategy, Stratified by AF Type

	First Cardiovascular Hospitalization					
Subgroup	Rhythm Control Events	Rhythm Control Rate*	Rate Control Events	Rate Control Rate*	Adjusted HR* (95% CI)	p Value
First detected/new onset AF	47	17.71	88	20.60	0.81 (0.54–1.21)	0.2964
Recurrent paroxysmal AF	745	18.72	816	16.55	1.17 (1.03–1.34)	**0.0164**
Recurrent persistent AF	200	23.07	271	13.40	1.49 (1.20–1.84)	**0.0003**

*Hazard ratio of rhythm control relative to rate control. Results are from inverse propensity weighted models. The p value for interaction between atrial fibrillation (AF) type and AF management strategy for outcome of first cardiovascular hospitalization, 0.012. **Bolded** values reflect 2-tailed $p < 0.05$.

CI = confidence interval; HR = hazard ratio.

the respective strategies in suppressing atrial fibrillation or controlling heart rate was much more likely with rhythm control. RECORDAF had fewer incident cardiovascular events during a shorter 1-year follow-up, and unsurprisingly the AF management strategy did not independently predict occurrence of adverse clinical events pooled together. Interestingly, the RECORDAF registry had a majority of patients on rhythm control strategy (54.9%), in contrast to our ORBIT-AF registry with a smaller proportion on rhythm control (40.9%).

ROLE FOR A RHYTHM CONTROL STRATEGY. Randomized clinical trials on AF have shown no influence on survival, stroke or heart failure with rhythm control using antiarrhythmic drugs and/or cardioversions for paroxysmal or persistent AF (4–7). Antiarrhythmic drugs can have cardiovascular adverse effects and these trials should have impacted the approach to using them to minimize unfavorable outcomes. However, after adjusting for confounders, our results support the applicability of prior clinical trials and guideline recommendations in contemporary practice (1). Current guidelines do not routinely recommend a rhythm control strategy for reducing the risk of mortality, stroke or heart failure (1). Rhythm control, however, may lead to improvements in quality of life, and in physical/metal disability scores (1–3); and current guidelines state that rhythm control should be considered for alleviating symptoms due to AF (1).

Although rhythm control was not statistically superior to rate control strategy in our registry, we observed trends towards improvements in all outcomes except cardiovascular hospitalizations. In particular, there was a trend toward reduction in overall mortality as well as reduction in composite of death, stroke, non-CNS embolism, and TIA. Although we cannot exclude the influence of chance or unmeasured confounding, these trends may suggest a role for rhythm control strategy in specific subgroups of patients that need to be identified. We did not observe a difference in the new diagnosis of heart failure between the rhythm control and rate control groups. This finding, however, does not preclude a role for rhythm control in patients presenting with congestive heart failure presumed secondary to previously undiagnosed AF.

ANTIARRHYTHMIC DRUGS AND CONGESTIVE HEART FAILURE. We did not observe any increase in new-onset congestive heart failure with rhythm control strategy. In the RECORDAF registry the rate of hospitalizations for heart failure was lower with rhythm control strategy, presumably on account of better controlled heart rates (11). Regardless, antiarrhythmic drugs should be used in patients with structural heart disease with caution due to risk of ventricular proarrhythmia. In the AF-CHF trial of AF patients with left ventricular ejection fraction ≤35%, there was no evidence of increased mortality with rhythm control (6). Notably, 82% of patients received amiodarone as the antiarrhythmic drug, and literature supports no increased mortality with amiodarone in AF patients (16).

RHYTHM CONTROL AND CARDIOVASCULAR HOSPITALIZATIONS. There were 24% independently higher first cardiovascular hospitalizations in the rhythm control group compared to rate control. The increase in hospitalizations among rhythm control patients was more marked for those with persistent AF. It is unclear if the cause for excess hospitalizations was for initiating/switching antiarrhythmic drugs with in-hospital heart rhythm monitoring or need for cardioversions/ablation procedures, or related to increase in cardiovascular adverse events. Our results are consistent with the RECORDAF registry, where there were higher elective hospitalizations with rhythm control strategy, though there was no increase in hospitalizations due to adverse cardiovascular events, and in fact a lower risk of heart failure hospitalizations (11).

ROLE OF LEFT ATRIAL ABLATION. Catheter-based or surgical left atrial ablation has emerged as an alternative to antiarrhythmic drug therapy for maintenance of sinus rhythm, potentially with higher efficacy and few long-term complications (1,17,18). Only a minority (13.1%) of our rhythm control patients had undergone catheter or surgical ablation of AF and most (72.6%) received antiarrhythmic drug therapy. Therefore, this analysis largely is a comparison of antiarrhythmic drugs to rate control drugs. Thus, even though rhythm control was not independently associated with improved survival, reduction of embolic events, or heart failure, these conclusions cannot be applied to an ablative approach to maintain sinus rhythm. Catheter ablation improves AF symptoms and quality of life and may result in reduced risk of thromboembolism (2,3,19–22). Several ongoing large clinical trials will assess the impact of ablation on cardiovascular outcomes and mortality, including the CABANA (Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial) trial (NCT00911508) comparing AF ablation with antiarrhythmic drugs, and the EAST (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) trial comparing a graduated rhythm control strategy with drugs followed by AF ablation with standard rate control based management (NCT01288352).

STUDY LIMITATIONS. The ORBIT-AF registry is a voluntary, observational study and susceptible to inherent limitations of such methods including residual confounding and confounding by unmeasured variables. The treatment assignment was not randomized and is quite likely influenced by baseline confounding factors that can be accounted for only partially. Even though the ORBIT-AF trial was designed to include a wide spectrum of AF patients across different practice setting, selection bias may exist. While the cohort is a contemporary population, nonpharmacologic methods of rhythm control, which may provide superior outcomes compared with antiarrhythmic drugs, remained a relatively small percentage of rhythm control therapies. ORBIT-AF is an observational registry, and choice of therapeutic treatment and drug selection may or may not have been consistent with the recommended guidelines.

CONCLUSIONS

This community-based evaluation of rhythm control versus rate control strategy for management of AF supports and reaffirms the evidence garnered from randomized clinical trials. Rhythm control is not associated with reduction in cardiovascular death, thromboembolism, new-onset heart failure, major bleeding, or all-cause mortality relative to rate control. Rhythm control patients experience more cardiovascular hospitalizations, possibly related to elective hospitalizations for changes in antiarrhythmic drug regimen or procedures (e.g., cardioversion, catheter ablation). Therefore, these findings support current guideline recommendations that the primary indication for rhythm control therapy is for the reduction of symptoms and improvement in quality of life.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Physicians can educate their patients that there is no benefit in terms of incident stroke, heart failure, and death with a rhythm control strategy with antiarrhythmic drugs when compared to rate control for AF. Notwithstanding the circumstances of hospital admission, elective or otherwise, rhythm control with antiarrhythmic drugs entails a higher rate of hospitalizations.

TRANSLATIONAL OUTLOOK: The findings from analysis of this prospectively maintained contemporary AF registry are consistent with results from prior randomized trials comparing rhythm control with rate control. Whether catheter ablation of atrial fibrillation instead of use of antiarrhythmic drugs impacts hard clinical outcomes is being evaluated with ongoing large multicenter randomized clinical trials.

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