Cardiac Rhythm Disorders

Functional Status in Rate- Versus Rhythm-Control Strategies for Atrial Fibrillation

Results of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Functional Status Substudy

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OBJECTIVES	The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) functional status substudy aimed to test the hypothesis that functional status is similar in rate-control and rhythm-control strategies.
BACKGROUND	Randomized studies, including the AFFIRM study, have failed to demonstrate survival benefits between rate-control and rhythm-control strategies for atrial fibrillation (AF). However, AF may cause functional capacity or cognitive impairment that might justify maintenance of sinus rhythm.
METHODS	Investigators of the AFFIRM study enrolled 4,060 patients with AF who required long-term therapy and who were 65 years of age or older or who had another risk factor for stroke or death. New York Heart Association functional class (NYHA-FC) and Canadian Cardiovascular Society Angina Classification were assessed at initial and each follow-up visit. From 22 randomly chosen functional status substudy sites, 245 participants underwent 6-min walk tests and Mini-Mental State Examination (MMSE) at initial, two-month, and yearly visits. Patients were assigned randomly to rate-controlling drugs, allowing AF to persist, or rhythm-controlling antiarrhythmic drugs, to maintain sinus rhythm.
RESULTS	The NYHA-FC worsened with time in both rate-control and rhythm-control groups, with no differences between groups. Presence of AF was associated with worse NYHA-FC ($p < 0.0001$). No differences were observed in Canadian Cardiovascular Society Angina Classification or MMSE scores. Six-minute walk distance improved over time in both study arms. On average, walk distance was 94 feet greater in the rhythm-control group (adjusted $p = 0.049$).
CONCLUSIONS	Modest improvement in 6-min walk distance was noted in the rhythm-control arm. Presence of AF was associated with worse NYHA-FC. No difference in cognitive function was detected. (J Am Coll Cardiol 2005;46:1891–9) © 2005 by the American College of Cardiology Foundation

Atrial fibrillation (AF) may cause significant morbidity, including the impairment of functional status. Exercise capacity may be limited by decreases in cardiac output from

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poorly controlled ventricular rates, loss of atrioventricular synchrony, or disability from stroke or other thromboem-

bolic complications (1–3). Additionally, impaired cognitive function has been reported (4–9), potentially related to silent embolic strokes or decreases in cerebral blood flow (10,11).

Functional status may be assessed by standard indices, including the New York Heart Association classification of functional capacity (NYHA-FC) (12,13) or Canadian Cardiovascular Society angina classification (CCS-AC) (13,14). Six-minute walk tests have been used to assess functional status in patients with cardiovascular and pulmonary diseases, including congestive heart failure (CHF) (15–17) and AF (18). The Mini-Mental State Examination (MMSE), a standardized test of cognition (19–21), has been used in intervention studies to monitor treatment effects and in AF studies to evaluate cognition (4–8,22).

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study (23,24), which assigned patients with AF randomly to rate-control versus

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Abbreviations and Acronyms
AF        = atrial fibrillation
AFFIRM    = Atrial Fibrillation Follow-up Investigation
            of Rhythm Management
CAD       = coronary artery disease
CCS-AC    = Canadian Cardiovascular Society angina
            classification
CHF       = congestive heart failure
LVEF      = left ventricular ejection fraction
MMSE      = Mini-Mental State Examination
NYHA-FC   = New York Heart Association functional
            class
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rhythm-control strategies, showed no significant difference in mortality between these approaches for AF. In light of this finding, morbidity or other clinical factors, such as functional status, may determine which strategy is most appropriate for patients with AF.

Functional status was assessed in a prospective, prespecified substudy of AFFIRM study patients to test the hypothesis that functional status is similar in rate-control and rhythm-control strategies. The substudy aimed to determine whether differences in functional status outcome measurements were associated with randomized strategy or rhythm present at testing. The NYHA-FC and CCS-AC were assessed in all patients at enrollment and all follow-up visits. Serial 6-min walk tests and MMSEs were performed in a subgroup of patients.

METHODS

Design of the AFFIRM study. In the AFFIRM study, a multicenter, randomized trial comparing rate-control versus rhythm-control strategies for the treatment of AF (23–26), patients from 213 U.S. and Canadian sites were enrolled from November 1995 through October 1999. Follow-up ended October 31, 2001.

Patients included in the study were ≥65 years of age or had another risk factor for stroke or death. Documentation was required that sufficient AF had been present to require long-term therapy. Patients were candidates for anticoagulation therapy and eligible to undergo trials with at least two drugs in both treatment strategies. The protocol was approved by each site's institutional review board. All patients gave informed, written consent to participate in the main study and, if participating in the functional status substudy, also for this substudy.

In the rate-control strategy, beta-blockers, calcium channel blockers (verapamil or diltiazem), and/or digoxin were used at the treating physician's discretion. Heart rate control was assessed at rest and exercise, with target heart rates of ≤80 beats/min at rest and ≤110 beats/min during the 6-min walk tests (23–26).

In the rhythm-control strategy, antiarrhythmic drug use was selected by the treating clinician with specific guidelines for the use of antiarrhythmic drugs in the protocol (25).

Patients in the rhythm-control arm underwent cardioversion as needed. Anticoagulation was used in both strategies according to published guidelines.

Functional status substudy populations. The NYHA-FC, CCS-AC, and cardiac rhythm were assessed on all AFFIRM study patients at an initial and every follow-up visit. Prospective substudies of functional status and quality of life were conducted. Of 213 clinical sites participating in the AFFIRM study, 25% were selected randomly to participate in the quality of life substudy (27). Of the quality of life substudy sites, 22 sites randomly were selected to participate in the functional status substudy. Functional status substudy patients underwent the 6-min walk test and MMSE at the initial, 2-month, 1 year, and yearly follow-up visits thereafter up to 5 years.

Measurements. CHF AND ANGINA STATUS. The NYHA-FC, assessing CHF symptoms of dyspnea and fatigue, and CCS-AC, assessing anginal chest pain, were defined by standard scales, with the addition of a class 0 in each scale to signify no symptoms of CHF or angina (12–14,25,28). Initial assessments were made at the time of randomization or during an initial visit within 14 days of randomization. In patients who were randomized while hospitalized, status was assessed at discharge. Both the NYHA-FC and CCS-AC were assessed at each follow-up visit (two months, four months, and every four months thereafter up to five years).

COGNITIVE FUNCTION. The MMSE, a brief, quantified assessment of cognitive state, evaluates orientation, registration, attention, memory, and the ability to name, follow verbal and written commands, write a sentence, and copy a complex figure (19–21). The examination is scored on a 30-point scale. Higher scores indicate better performance. Tasks that could not be attempted because of physical impairment (e.g., vision, hearing, severe arthritis) were not added to the total score. Tasks that could not otherwise be attempted or completed were scored 0.

6-MIN WALK TEST. Six-minute walking tests were conducted in the standardized fashion (1,29–34). Distance walked during 6 min of self-paced walking and standing heart rates at baseline and at the end of the walk were recorded.

Sample size. Sample size calculations for the functional status subpopulation were computed based on the MMSE with 80% power to detect a 10% difference in scale (three points) and on the 6-min walk test with 80% power to detect a 25 meter (82 feet) difference. For both calculations, the required sample size to detect differences of this magnitude was fewer than 50 patients.

Statistical analysis. The primary analysis was an unadjusted intention-to-treat comparison between rate-control and rhythm-control strategies for NYHA-FC, CCS-AC, 6-min walk test distance, and MMSE scores. Additionally, intention-to-treat comparisons were performed adjusting for imbalances of baseline covariates. Data also were ana-

lyzed by the actual rhythm present at the time of evaluation in adjusted analyses not including treatment arm. Covariates used in adjusted models included prespecified subgroups (age, qualifying AF episode being the first episode of AF, gender, rhythm at randomization, duration of qualifying episode ≥2 days, normal left ventricular ejection fraction [LVEF], presence of coronary artery disease [CAD], history of CHF or hypertension), as well as other variables that could be related to functional status (history of stroke or transient ischemic attack, diabetes, smoking, and college education). Data are reported as mean ± standard deviation unless otherwise noted. Differences were considered statistically significant at p values <0.05.

Baseline characteristics were compared with the chi-square and Student *t* tests. Analyses using all visits were based on repeated measures models. These statistical analyses used generalized estimating equations, a statistical technique that combines all longitudinal data into one model and accounts for the nonindependence of within-patient observations (35). The correlation structure for within-patient observations was assumed to be exchangeable (all off-diagonal elements equal). Unadjusted analyses of all variables but NYHA-FC and CCS-AC included visit as a categorical variable so we could analyze group differences. Because of the greater number of visits with assessments of NYHA-FC and CCS-AC, unadjusted analyses of these variables used time as a continuous variable, based on years since randomization. Adjusted analyses used a similar continuous variable for the time effect and assessed change over the course of time by including two-way interaction terms.

RESULTS

From 213 sites, 4,060 patients were enrolled in the AFFIRM study (24); 245 patients participated in the functional status substudy. Functional status substudy analyses excluded 19 patients enrolled at substudy sites who declined to participate in functional status assessments. All AFFIRM study patients (n = 4,060) participated in NYHA-FC and CCS-AC assessments at each visit.

Patient characteristics. Functional status substudy subjects were similar to the rest of the AFFIRM study population (Table 1), except that compared with subjects not in the substudy, the substudy group had a lower percentage of females (33% vs. 40%, p = 0.03) and ethnic minorities (7% vs. 12%, p = 0.04) and a higher proportion with warfarin use at baseline (93% vs. 84%, p = 0.0003), previous antiarrhythmic drug failure (25% vs. 17%, p = 0.002), and class IA antiarrhythmic drug use (14% vs. 7%, p = 0.0007). No significant differences between rate and rhythm control groups were present in the total AFFIRM study group (24) nor in the substudy (Table 1, p values all >0.05). Mean follow-up time was 3.60 ± 1.2 years for patients in the substudy and 3.48 ± 1.3 years for the entire AFFIRM study. The number and percentage of substudy patients in sinus rhythm at their final

visit were 45 of 125 (36%) in the rate-control and 78 of 120 (65%) in the rhythm-control arms (chi-square p < 0.0001).

NYHA-FC. INTENTION-TO-TREAT UNADJUSTED ANALYSIS. Mean NYHA-FC worsened significantly over the course of time in both rate-control and the rhythm-control arms of the entire study (n = 4,060, p < 0.0001) (Fig. 1A). No significant differences were observed between treatment arms across all visits or at any specific visit.

INTENTION-TO-TREAT ADJUSTED ANALYSIS. Adjusted analysis of NYHA-FC across all visits demonstrated no significant differences between rate-control and rhythm-control patients. Covariates significantly associated with worse NYHA-FC across all visits included history of CHF (p < 0.0001), age ≥65 years (p = 0.0005), diabetes (p = 0.0017), abnormal LVEF (p < 0.0001), and CAD (p < 0.0001). History of CHF was significantly associated with worsening NYHA-FC over the course of time (p = 0.0045).

ADJUSTED ANALYSIS BY CURRENT RHYTHM. Adjusted analysis of NHYA-FC across all visits including current rhythm (AF or sinus rhythm) at each visit demonstrated that current AF was significantly associated with worse NYHA-FC (p < 0.0001, 95% confidence interval 0.0770 to 0.1218) (Fig. 1B). Other significant covariates included CHF (p < 0.0001), age ≥65 years (p = 0.0074), male gender (p < 0.0001), diabetes (p = 0.0019), abnormal LVEF (p < 0.0001), and CAD (p < 0.0001). History of CHF was the only covariate significantly associated with worsening NYHA-FC over the course of time (p = 0.0055).

CCS-AC. INTENTION-TO-TREAT UNADJUSTED ANALYSIS. In the AFFIRM study, only 9% of rate-control and 10% of rhythm control patients had anginal symptoms at the initial visits. There were no significant differences between the two treatment arms across all visits or at any specific visit.

INTENTION-TO-TREAT ADJUSTED ANALYSIS. Covariates significantly associated with worse CCS-AC included history of CAD (p < 0.0001), duration of qualifying episode ≥2 days (p < 0.0001), diabetes (p = 0.0093), CHF (p < 0.0001), and prior stroke or transient ischemic attack (p = 0.024). The CCS-AC did not significantly change over the course of time, and no variables were significantly associated with change over the course of time. Treatment arm was not significantly associated with CCS-AC across all visits or over the course of time.

ADJUSTED ANALYSIS BY CURRENT RHYTHM. In adjusted models including current rhythm at each visit, presence of AF was not significantly associated with CCS-AC.

Cognitive function: MMSE INTENTION-TO-TREAT UNADJUSTED ANALYSIS. At the initial visit, the mean MMSE scores were higher for rate-control (28.3 ± 2.2) compared with rhythm-control (27.3 ± 2.6; p = 0.0054) (Table 2). There were no significant differences between arms at any follow-up visit or across all visits.

Table 1. Baseline Patient Characteristics

	All Patients (n = 4060)	Patients in FS (n = 245, 6%)	Patients Not in FS (n = 3815, 94%)	p Value*	FS Patients Rate-Control (n = 125)	FS Patients Rhythm-Control (n = 120)
Treatment arm				0.72		
Rate-control	2,027 (50)	125 (51)	1,902 (50)			
Rhythm-control	2,033 (50)	120 (49)	1,913 (50)			
Age, yrs (mean ± SD)	69.7 ± 9.0	69.8 ± 8.8	69.7 ± 9.0	0.91	69.8 ± 9.4	69.9 ± 8.3
Age >65 yrs	3,091 (76)	196 (80)	2,895 (76)	0.14	102 (82)	94 (78)
Gender, female sex	1,594 (39)	80 (33)	1,514 (40)	0.03	45 (36)	35 (29)
Ethnic minority group	461 (11)	18 (7)	443 (12)	0.04	8 (6)	10 (8)
Predominant cardiac diagnosis				0.13		
CAD	1,059 (26)	62 (25)	997 (26)		33 (26)	29 (24)
Cardiomyopathy	194 (5)	8 (3)	186 (5)		4 (3)	4 (3)
HTN	2,063 (51)	133 (54)	1,930 (51)		68 (54)	65 (54)
Valvular disease	198 (5)	8 (3)	190 (5)		1 (1)	7 (6)
Other	42 (1)	6 (2)	36 (1)		4 (3)	2 (2)
No apparent heart disease	504 (12)	28 (11)	476 (12)		15 (12)	13 (11)
History of CHF	939 (23)	51 (21)	888 (23)	0.38	24 (19)	27 (23)
History of CAD	1,551 (38)	93 (38)	1,458 (38)	0.94	52 (42)	41 (34)
History of diabetes	813 (20)	47 (19)	766 (20)	0.73	27 (22)	20 (17)
History of stroke	542 (13)	26 (11)	516 (14)	0.19	12 (10)	14 (12)
History of smoking	496 (12)	31 (13)	465 (12)	0.83	14 (11)	17 (14)
LVEF (mean ± SD)	54.7 ± 13.5	53.6 ± 12.4	54.8 ± 13.5	0.51	56.1 ± 11.1	50.6 ± 13.4
Normal LVEF	2,244 (74)	136 (75)	2,108 (74)	0.82	70 (78)	66 (72)
Moderate-severe LV dysfunction	396 (13)	23 (13)	373 (13)	0.86	7 (8)	16 (17)
Normal left atrial size	1,103 (35)	63 (35)	1040 (35)	0.85	30 (34)	33 (35)
Warfarin use at baseline	3,434 (85)	227 (93)	3,207 (84)	0.0003	119 (95)	108 (90)
Previous antiarrhythmic drug failure	713 (18)	61 (25)	652 (17)	0.002	30 (24)	31 (26)
Duration of qualifying AF episode						
≥2 days	2,808 (69)	170 (69)	2,638 (69)	0.94	87 (70)	83 (69)
Qualifying episode first AF episode	1,391 (36)	75 (32)	1,316 (36)	0.18	39 (32)	36 (31)
In AF at baseline	1,554 (38)	104 (42)	1,450 (38)	0.17	62 (50)	42 (35)
Drug started or continued						
Class I	524 (17)	40 (22)	484 (16)	0.06		40 (36)
Class IA	239 (8)	26 (14)	213 (7)	0.0007		26 (33)
Class IC	273 (9)	13 (7)	260 (9)	0.41		13 (12)
Class III	1,348 (43)	72 (39)	1,276 (43)	0.26		72 (65)
Calcium channel blocker	1,025 (32)	55 (29)	970 (33)	0.26	45 (38)	10 (13)
Beta-adrenergic blocker	1,196 (38)	80 (41)	1,116 (37)	0.26	61 (52)	19 (25)
Digoxin	1,377 (43)	81 (43)	1,296 (43)	0.76	54 (46)	27 (36)

n (%) except where noted. *p value reflects comparison of patients in FS substudy to patients not in substudy. Echocardiograms were obtained in 3,311 patients (overall AFFIRM study: 1,650 rate-control, 1,661 rhythm-control; functional status substudy: 100 rate-control, 100 rhythm-control). Left atrial size was unknown in 242 (71 functional status patients); LV function and LVEF were unknown in 335 patients (65 functional status patients). Normal LV function was defined as LVEF ≥50% and moderate-severe LV dysfunction as LVEF <40%.

AF = atrial fibrillation; CAD = coronary artery disease; CHF = congestive heart failure; FS = Functional Status substudy; HTN = hypertension; LV = left ventricle; LVEF = left ventricular ejection fraction; SD = standard deviation.

INTENTION-TO-TREAT ADJUSTED ANALYSIS. College education was the only covariate significantly associated with MMSE. Patients with college education scored higher, on average, than those without (p < 0.0001). Age was the only significant covariate associated with change in MMSE score over the course of time (p = 0.02). Patients ≥65 years old experienced a decrease of 0.28 points per year more than patients <65 years of age.

ADJUSTED ANALYSIS BY CURRENT RHYTHM. Current AF at each visit was not a significant covariate (Table 2). Warfarin use was not significantly associated with MMSE scores.

Functional capacity: 6-min walk test distance. **INTENTION-TO-TREAT UNADJUSTED ANALYSIS.** Average walk distance increased with time in both treatment strategies (Fig. 2A). Rhythm-control patients walked significantly more distance on average, compared with rate-control patients with differences of 118 feet more at the initial visit, 124 feet at two months and 124 feet at one year. Averaging across all visits, differences between the rate-control and the rhythm-control arms were borderline significant (p = 0.06), with rhythm-control patients walking on average 100 feet (8.5%) more than rate-control patients.

INTENTION-TO-TREAT ADJUSTED ANALYSIS. In adjusted analysis, walk distance across all visits was significantly and independently associated with treatment arm (p = 0.049, 95% confidence interval 0.4158 to 188.57 feet). Average walk distance was 94 feet (5.8%) more in the rhythm-control arm. Other significant covariates included diabetes (192 fewer feet, p = 0.0015), gender (females 187 fewer feet, p = 0.0006), CHF (228 fewer feet, p = 0.0001), and age <65 years (133 more feet, p = 0.023).
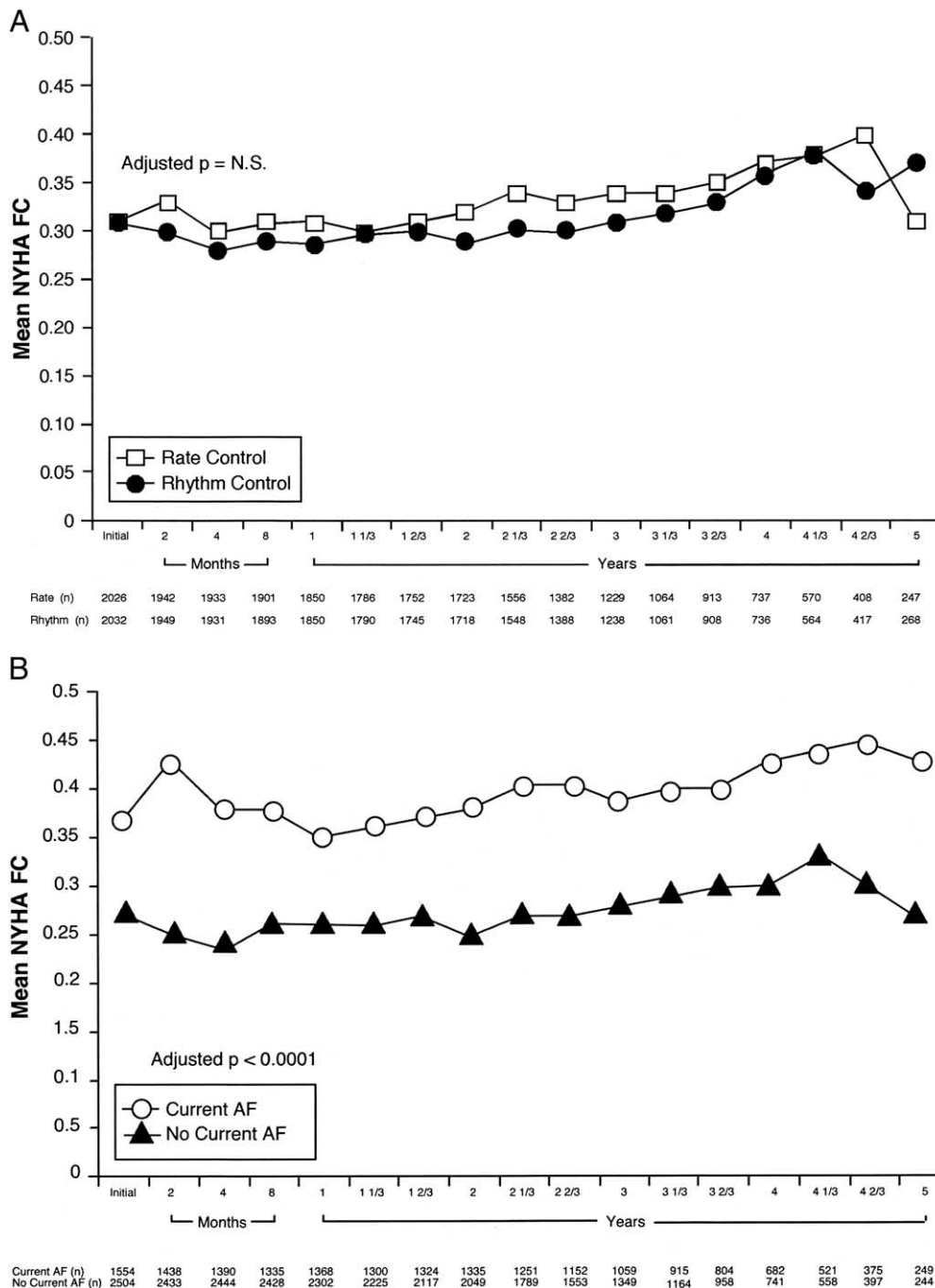
Figure 1. New York Heart Association functional class (NYHA-FC). Mean NYHA-FC at each visit. **(A)** Rate- versus rhythm-control randomized treatment. **(B)** Current atrial fibrillation (AF) status: current AF versus no current AF present at visit. The p values reflect comparisons between two groups from repeated measures analyses across all visits. N.S.= not significant.

ADJUSTED ANALYSIS BY CURRENT RHYTHM. Walk distance at each visit by current rhythm is shown in Figure 2B. In adjusted models, AF at each visit was not significantly associated with distance walked.

Functional capacity: 6-min walk test heart rates. **INTENTION-TO-TREAT UNADJUSTED ANALYSIS.** Mean pre-walk heart rates were significantly higher in the rate-control compared with rhythm-control group across all visits (average difference 3.6 beats/min, $p = 0.0058$).

Pre-walk heart rates in both groups decreased over the course of time (Table 3).

Mean post-walk heart rates in both rate-control and rhythm-control arms also decreased over time, decreasing on average 0.98 beats/min per year across both treatment groups ($p = 0.025$) (Table 3). Treatment group differences were not significantly different at any visit or across all visits. Change in heart rate during walk tests was not significantly different between treatment strategies.

Table 2. Mini-Mental State Examination (MMSE) Scores

	Initial	2 Months	1 Year	2 Years	3 Years	4 Years
A. MMSE by Rate Versus Rhythm Control Treatment Randomization*						
Rate	28.3 ± 2.2 (n = 116)	28.4 ± 2.0 (n = 109)	28.2 ± 2.2 (n = 107)	28.1 ± 2.1 (n = 83)	28.3 ± 2.3 (n = 58)	28.4 ± 2.3 (n = 39)
Rhythm	27.3 ± 2.6 (n = 116)	28.2 ± 2.1 (n = 107)	28.1 ± 2.0 (n = 95)	27.8 ± 2.7 (n = 83)	28.2 ± 2.3 (n = 66)	28.3 ± 3.0 (n = 33)
B. MMSE by Current Atrial Fibrillation Status†						
Current rhythm						
No atrial fibrillation	27.7 ± 2.4 (n = 131)	28.3 ± 2.1 (n = 124)	28.1 ± 2.2 (n = 109)	28.1 ± 2.5 (n = 95)	28.3 ± 2.3 (n = 69)	28.7 ± 1.8 (n = 31)
Atrial fibrillation	27.9 ± 2.4 (n = 101)	28.3 ± 2.0 (n = 92)	28.3 ± 2.0 (n = 93)	27.8 ± 2.4 (n = 71)	28.1 ± 2.3 (n = 55)	28.0 ± 3.1 (n = 41)

*$p = 0.24$; †$p = 0.31$. p values reflect group differences across all visits from unadjusted generalized estimating equations analyses, including visit as a categorical variable.
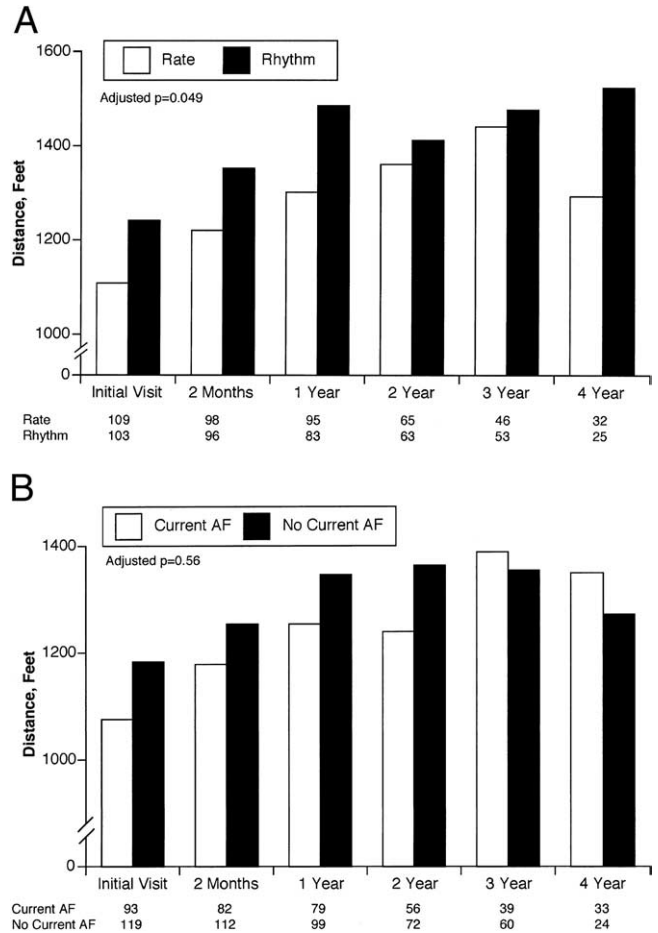

Figure 2. Six-minute walk test distance. **(A)** Rate- versus rhythm-control randomized treatment. **(B)** Current atrial fibrillation (AF) status: current AF versus no current AF present at visit. The p values reflect comparisons between two groups from repeated measures analyses across all visits.

INTENTION-TO-TREAT ADJUSTED ANALYSIS. In adjusted analyses, pre-walk heart rates were significantly higher in the rate-control compared with rhythm-control group (average difference 3.6 beats/min, $p = 0.004$), but there were no significant differences between groups in post-walk heart rates.

ADJUSTED ANALYSIS BY CURRENT RHYTHM. Including current rhythm in adjusted models, AF was associated with higher pre-walk (mean 11.5 beats/min higher, $p < 0.0001$) and post-walk (mean 12.7 beats/min higher, $p < 0.0001$) heart rates.

DISCUSSION

The AFFIRM study reported no significant survival benefits achieved from a rhythm-control compared with rate-control strategy in patients with AF and showed benefit for continuous anticoagulation with either treatment strategy (24). In the absence of a survival difference and with persisting necessity for anticoagulation, major reasons to treat AF may include relief of symptoms and improvement in functional status. In the current study,

Table 3. Heart Rates for Six-Minute Walk Test at Initial and Follow-Up Visits

		Initial	2 Months	1 Year	2 Years	3 Years	4 Years
Rate-Control Versus Rhythm-Control Treatment Arm							
n	Rate	109	98	95	65	46	32
	Rhythm	105	96	83	63	53	25
HR pre-walk	Rate	75.8 ± 16	73.2 ± 13	72.9 ± 11	72.9 ± 13	69.4 ± 10	68.8 ± 10
p = 0.0057	Rhythm	74.0 ± 16	67.5 ± 12	67.1 ± 13	68.8 ± 15	68.4 ± 13	72.4 ± 14
HR post-walk	Rate	95.2 ± 24	89.8 ± 17	89.9 ± 15	90.4 ± 17	86.8 ± 14	86.3 ± 15
p = 0.13	Rhythm	93.8 ± 19	86.1 ± 17	86.4 ± 18	86.7 ± 18	85.5 ± 20	87.5 ± 18
HR post-walk-HR pre-walk	Rate	19.3 ± 15	16.6 ± 11	17.0 ± 11	17.4 ± 11	17.4 ± 10	17.5 ± 12
p = 0.45	Rhythm	19.8 ± 14	18.6 ± 12	19.3 ± 14	17.9 ± 11	17.1 ± 15	15.0 ± 13
Current AF Status							
n	No	119	112	99	72	60	24
	Yes	95	82	79	56	39	33
HR pre-walk	No	68.1 ± 12	65.3 ± 11	65.4 ± 11	65.5 ± 12	66.2 ± 12	64.0 ± 10
p < 0.0001	Yes	83.5 ± 16	77.2 ± 12	76.3 ± 11	77.8 ± 14	72.9 ± 10	75.1 ± 11
HR post-walk	No	85.8 ± 17	82.6 ± 17	83.0 ± 16	81.6 ± 14	82.6 ± 19	81.2 ± 16
p < 0.0001	Yes	105.5 ± 23	95.4 ± 15	94.9 ± 16	97.6 ± 18	91.6 ± 13	90.9 ± 15
HR post-walk-HR pre-walk	No	17.6 ± 12	17.3 ± 12	17.6 ± 13	16.1 ± 10	16.4 ± 13	17.2 ± 15
p = 0.0061	Yes	22.0 ± 16	18.1 ± 11	18.6 ± 11	19.8 ± 12	18.7 ± 11	15.9 ± 10

All p values reflect group differences across all visits from unadjusted generalized estimating equations analyses, including visit as a categorical variable
HR = heart rate in beats/min.

modestly longer 6-min walk distances were noted with the rhythm-control strategy. The presence of AF was significantly associated with worse NYHA-FC and higher heart rates. However, no difference in cognitive function was detected.

NYHA-FC. The NYHA-FC slightly increased over time in both rate- and rhythm-control patients. Although no significant differences between treatment groups were observed in NYHA-FC, the presence of current AF at follow-up visits was significantly associated with worse NYHA-FC. Part of this paradox between the goal of maintaining sinus rhythm and the actual presence of sinus rhythm may be related to the inefficacy of antiarrhythmic drugs to achieve their goal of maintaining sinus rhythm.

CCS-AC. Angina pectoris was uncommon in AFFIRM, consistent with other studies showing chest pain to be an uncommon symptom in AF (36). Few patients in the AFFIRM study had angina at the beginning of the study. No differences in angina classification were detected between treatment groups.

Cognitive function. Adjusted MMSE scores did not differ significantly between treatment groups, in analyses based on actual rhythm present at follow-up, or after adding warfarin use to the analyses.

Age, although not previous CVA, was associated with change in scores over time. In a previous study of elderly patients with nonvalvular chronic AF, age and number of lacunar lesions were associated with lower MMSE scores (22). Previous reports of cognitive dysfunction associated with AF studied patient cohorts in which the use or dose of anticoagulation was low (22,37–39). Although there was a difference in anticoagulation use between the randomized arms of the AFFIRM study, anticoagulation use was high overall, with no significant difference in stroke rates between

groups, which may explain the lack of detection of differences in cognitive function in AF patients, if these differences depended upon the relative incidences of cerebrovascular events.

Walk testing. Functional status, as measured by 6-min walk test distance, improved in both treatment arms. Walk distance across all visits was modestly although significantly longer in the rhythm-control group. These results are similar to those reported in the Pharmacological Intervention in Atrial Fibrillation (PIAF) study (18) of 252 patients randomized to rate versus rhythm-control. Walk distances were on average shorter in the AFFIRM study, but the AFFIRM study population was older (mean age 70 years) than in PIAF (mean age 60 years). Although there appeared to be a trend toward longer walk distances in patients in sinus rhythm compared with AF up through year 2, this difference was not sustained at years 3 and 4. The reason for this is unclear, particularly as prewalk and postwalk heart rate control did not appear worse on average at later years, although differences in the type of medications used in the rate- and rhythm-control groups could have been contributory.

Whether the mean difference of approximately 100 feet (8.5%) between rate-control and rhythm-control walk distance is clinically significant is uncertain. In a study of 45 older patients with CHF, the mean difference in 6-min walk distance associated with clinical differences in patient perception of worsening was 43 meters (141 feet) (17). In studies of biventricular pacing in heart failure patients, clinical benefit was reported with 6-min walk distance differences of 29 meters (95 feet) in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial (40) and 38.5 meters (126 feet) at three months and 42 meters (138 feet) at six months in the Comparison of Medical

Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial (41). Among studies reporting differences as a percentage of walk distances, benefits with biventricular pacing range from 17% to 32%, corresponding to walk distance differences of 29 to 93 meters (95 to 305 feet) (39,42–44). Detection of changes in 6-min walk distances may be restricted by limited responsiveness of the measure (45).

Pre-walk heart rates were significantly higher in the rate-control arm. Moreover, current AF was strongly associated with both higher pre-walk and post-walk heart rates compared with sinus rhythm. These differences persisted over time and could have contributed to the shorter walk distances observed in patients in the rate-control group. It is unclear whether targeting to lower heart rate levels would have improved walk distances or achieved other functional status benefits in the rate control strategy. Moreover, it is uncertain whether higher heart rates or AF itself led to the differences observed in walk distance or functional class.

Study limitations. Several factors may have affected the impact of treatment strategies on functional status. Patients with frequent or severe AF symptoms may not have been enrolled, and it is unknown how more symptomatic patients would have responded to treatment strategies. It is also possible that more-stringent heart rate control in the rate control arm would have achieved better functional status.

True baseline assessment of functional status before randomization was not available in all patients because initial visits for functional status assessments were dissimilar to randomization dates in 34% of patients. At initial functional status visits, 52% of rate-control and 35% of rhythm-control patients were in AF (p = 0.012), suggesting an effect of prescribed treatment before initial functional status assessment. Thus, changes in functional status parameters from initial assessments cannot necessarily infer change from a baseline prerandomization state. This limitation may particularly be true for walk test results.

Relative insensitivity of the MMSE to detect changes in cognitive function, especially near the higher end of the scale, may have limited these results. However, this instrument was a standard measure of cognitive function at the time when the AFFIRM study was designed. Finally, in the AFFIRM study, assessments were not blinded. It is possible that knowledge of the randomized strategy or the presence of AF resulted in biased functional status evaluations.

Conclusions. The NYHA-FC gradually worsened with time in both rate and rhythm-control groups and was significantly worse if AF was present at follow-up. Six-min walk test distance improved over the course of time in patients treated with either strategy and was modestly longer in the rhythm-control patients. Higher resting pre-walk heart rates were observed in rate-control strategy patients; pre-walk and post-walk heart rates were higher in patients with current AF at testing. It is unclear whether lower heart rate targets in the rate control strategy would have improved walk distances. Cognitive function, as mea-

sured by MMSE scores, did not significantly differ over the course of time in patients treated with either strategy. Although a rhythm-control approach used to treat AF does not improve survival, this strategy might be appropriate for patients with AF who remain symptomatic despite rate control, as some incremental improvement in functional status may be achievable.

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REFERENCES

1. Lok NS, Lau CP. Oxygen uptake kinetics and cardiopulmonary performance in lone atrial fibrillation and the effects of sotalol. Chest 1997;111:934–40.
2. Ostermaier RH, Lampert S, Dalla Vecchia L, Ravid S. The effect of atrial fibrillation and the ventricular rate control on exercise capacity. Clin Cardiol 1997;20:23–7.
3. Pardaens K, Van Cleemput J, Vanhaecke J, Fagard RH. Atrial fibrillation is associated with a lower exercise capacity in male chronic heart failure patients. Heart 1997;78:564–8.
4. Sabatini T, Frisoni GB, Barbisoni P, Bellelli G, Rozzini R, Trabucchi M. Atrial fibrillation and cognitive disorders in older people. J Am Geriatr Soc 2000;48:387–90.
5. Kilander L, Andren B, Nyman H, Lind L, Boberg M, Lithell H. Atrial fibrillation is an independent determinant of low cognitive function: a cross-sectional study in elderly men. Stroke 1998;29: 1816–20.
6. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. Stroke 1997;28:316–21.
7. O'Connell JE, Gray CS, French JM, Robertson IH. Atrial fibrillation and cognitive function: case-control study. J Neurol Neurosurg Psychiatry 1998;65:386–9.
8. Farina E, Magni E, Ambrosini F, et al. Neuropsychological deficits in asymptomatic atrial fibrillation. Acta Neurol Scand 1997;96:310–6.
9. Stanley TO, Mackensen GB, Grocott HP, et al. The impact of postoperative atrial fibrillation on neurocognitive outcome after coronary artery bypass graft surgery. Anesth Analg 2002;94:290–5.
10. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22: 983–8.
11. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154: 1449–57.
12. The Criteria Committee of the New York Heart Association. Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis. 6th edition. New York, NY: New York Heart Association, Little, Brown, and Company, 1964.
13. Ganiats TG, Browner DK, Dittrich HC. Comparison of Quality of Well-Being scale and NYHA functional status classification in patients with atrial fibrillation. New York Heart Association. Am Heart J 1998;135:819–24.
14. Cox J, Naylor CD. The Canadian Cardiovascular Society grading scale for angina pectoris: is it time for refinements? Ann Intern Med 1992;117:677–83.
15. Hendrican MC, McKelvie RS, Smith T, et al. Functional capacity in patients with congestive heart failure. J Card Fail 2000;6:214–9.
16. Kavanagh T, Myers MG, Baigrie RS, Mertens DJ, Sawyer P, Shephard RJ. Quality of life and cardiorespiratory function in chronic heart failure: effects of 12 months' aerobic training. Heart 1996;76: 42–9.

17. O'Keeffe ST, Lye M, Donnellan C, Carmichael DN. Reproducibility and responsiveness of quality of life assessment and six minute walk test in elderly heart failure patients. Heart 1998;80:377–82.

18. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation—Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. Lancet 2000;356:1789–94.

19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

20. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993;269:2386–91.

21. Bassett SS, Folstein MF. Cognitive impairment and functional disability in the absence of psychiatric diagnosis. Psychol Med 1991;21:77–84.

22. Zito M, Muscari A, Marini E, Di Iorio A, Puddu GM, Abate G. Silent lacunar infarcts in elderly patients with chronic nonvalvular atrial fibrillation. Aging (Milano) 1996;8:341–6.

23. Wyse DG. The AFFIRM trial: main trial and substudies—what can we expect? J Interv Card Electrophysiol 2000;4 Suppl 1:171–6.

24. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825–33.

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

26. The AFFIRM Investigators. Baseline characteristics of patients with atrial fibrillation: the AFFIRM study. Am Heart J 2002;143:991–1001.

27. The AFFIRM Investigators. Quality of life in atrial fibrillation: the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study. Am Heart J 2005;149:112–20.

28. Campeau L. Grading of angina pectoris. Circulation 1976;54:522–3.

29. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7.

30. Cahalin LP, Mathier MA, Semigran MJ, Dec GW, DiSalvo TG. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. Chest 1996;110:325–32.

31. Langenfeld H, Schneider B, Grimm W, et al. The six-minute walk—an adequate exercise test for pacemaker patients? Pacing Clin Electrophysiol 1990;13:1761–5.

32. Opasich C, Pinna GD, Mazza A, et al. Six-minute walking performance in patients with moderate-to-severe heart failure; is it a useful indicator in clinical practice? Eur Heart J 2001;22:488–96.

33. Provenier F, Jordaens L. Evaluation of six minute walking test in patients with single chamber rate responsive pacemakers. Br Heart J 1994;72:192–6.

34. Shah MR, Hasselblad V, Gheorghiade M, et al. Prognostic usefulness of the six-minute walk in patients with advanced congestive heart failure secondary to ischemic or nonischemic cardiomyopathy. Am J Cardiol 2001;88:987–93.

35. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22.

36. Levy S, Maarek M, Coumel P, et al. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The College of French Cardiologists. Circulation 1999;99:3028–35.

37. Ezekowitz MD, James KE, Nazarian SM, et al. Silent cerebral infarction in patients with nonrheumatic atrial fibrillation. The Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. Circulation 1995;92:2178–82.

38. Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. N Engl J Med 1992;327:1406–12.

39. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348:1215–22.

40. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–53.

41. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50.

42. Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. J Am Coll Cardiol 2002;40:111–8.

43. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873–80.

44. Kuhlkamp V. Initial experience with an implantable cardioverter-defibrillator incorporating cardiac resynchronization therapy. J Am Coll Cardiol 2002;39:790–7.

45. Demers C, McKelvie RS, Negassa A, Yusuf S. Reliability, validity, and responsiveness of the six-minute walk test in patients with heart failure. Am Heart J 2001;142:698–703.