

Real-Life Observations of Clinical Outcomes With Rhythm- and Rate-Control Therapies for Atrial Fibrillation

RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation)

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Objectives	RECORDAF is the first worldwide, prospective, observational survey of management of atrial fibrillation (AF) in unselected, community-based patients.
Background	Primary outcomes were therapeutic success and clinical outcomes associated with rhythm-control and rate-control strategies.
Methods	Patients with recent-onset AF were included (n = 5,604). Treatment strategy (rhythm control or rate control) was noted at baseline. Follow-up was 12 months. Therapeutic success required that strategy was unchanged without clinical events. Further maintenance of sinus rhythm was required in the rhythm-control group, and heart rate ≤ 80 beats/min in the rate-control group.
Results	Data from 5,171 patients were assessable. Therapeutic success was 54% overall (rhythm control 60% vs. rate control 47%), a result driven by control of AF: rhythm control, 81% vs. rate control, 74%. After adjustment for propensity score quintiles, the rhythm-control strategy was significantly related to superior therapeutic success (odds ratio: 1.34, 95% confidence interval: 1.15 to 1.55; p = 0.0002). Clinical events occurred in 18% of patients. The arrhythmia management strategy was not predictive of clinical events. The type (persistent), presence at baseline visit, and duration (>3 months) of AF, together with age older than 75 years and the presence of heart failure, predicted progression to permanent AF. The choice of rhythm control reduced the likelihood of AF progression (odds ratio: 0.20, 95% confidence interval: 0.17 to 0.25; p < 0.0001).
Conclusions	Clinical outcomes in AF patients were driven mainly by hospitalizations for arrhythmia/proarrhythmia and other cardiovascular causes, but not by the choice of rate or rhythm strategy. Rhythm-control patients progressed less rapidly to permanent AF. (J Am Coll Cardiol 2011;58:493–501) © 2011 by the American College of Cardiology Foundation

In addition to appropriate antithrombotic treatment, 2 broad strategies are used to manage recurrent episodes of

atrial fibrillation (AF): rhythm control, which implies the restoration and maintenance of sinus rhythm, and rate

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Abbreviations and Acronyms

AF = atrial fibrillation
CAD = coronary artery disease
CI = confidence interval
ECG = electrocardiogram
MI = myocardial infarction
OR = odds ratio
TIA = transient ischemic attack

control, which involves keeping the ventricular rate at a physiological level while allowing the atria to continue to fibrillate. However, contrary to expectation, accumulated trial data indicated that for the patient populations and specific therapies evaluated, a rhythm-control strategy was not superior to a rate-control strategy with regard to various major cardiovascular endpoints (1–3).

Because enrollment is limited to patients who can be randomized to either study arm and physicians must condone and support the allocated treatment for the duration of the study, clinical trials do not always reflect usual clinical practice. In addition, trials exploring the value of a treatment strategy are critically dependent for their interpretation on the ability of the strategy to achieve its intermediate goal, in this instance, maintenance of sinus rhythm or persistence of adequate rate control. Some have criticized the rate-versus-rhythm trials for such failures (4).

Although not protected by randomization, registry data may provide complementary information to resolve further the choice of treatment strategy. The RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation) was established to investigate “real-world” treatment of patients assigned, on clinical grounds, to a rate-control or rhythm-control strategy. The RECORDAF is the first worldwide, 1-year observational, longitudinal study of the treatment of patients with recently diagnosed paroxysmal or persistent AF.

Methods

The primary objectives of the RECORDAF were to prospectively assess therapeutic success and clinical outcomes with rhythm- and rate-control strategies. Physicians were randomly selected from an exhaustive global list of office- or hospital-based (university/nonuniversity, private/clinic) cardiologists. Consecutive patients age 18 years and older were considered for enrollment if they presented with AF or a history of AF (≤ 1 year from diagnosis, irrespective of whether AF was treated and of the rhythm at inclusion) received a diagnosis based on a standard electrocardiogram (ECG) or Holter monitoring and were eligible for pharmacological treatment of AF by rhythm- or rate-control agents. Exclusion criteria included permanent AF or a transient/reversible cause of AF. All patients signed an informed consent form. Data were collected at baseline (visit 0), 6 ± 2 months (visit 1: nonmandatory), and 12 ± 3 months (visit 2).

Management of AF was considered a therapeutic success if the following conditions were met: 1) for the rhythm-control strategy, AF was said to be controlled if the patient

was in sinus rhythm on the ECG at the 12-month visit; 2) for the rate-control strategy, the patient had a resting heart rate of ≤ 80 beats/min on the ECG at the 12-month visit. Therapeutic success also required that no crossover between strategies had been made and no clinical outcome had occurred between the baseline and 12-month visits.

Multiple clinical outcomes were measured to evaluate in detail the impact of cardiovascular risk factors (including the control of AF). Hence, the occurrence of at least 1 of the following events was counted between baseline and 12 months: cardiovascular death; stroke, or transient ischemic attack (TIA) leading to hospitalization; myocardial infarction (MI); hospitalization for arrhythmic/proarrhythmic events, hospitalization for complications of ablation procedures, but not the actual procedures; and other cardiovascular events (congestive heart failure, unstable angina, peripheral ischemic events, percutaneous coronary intervention, coronary artery bypass graft, valvular surgery, carotid angioplasty, carotid endarterectomy, other cardiac or vascular surgery). Cardiovascular death reported until the end of the 15th month after baseline was counted as a clinical outcome in the 12-month analysis.

To estimate a success rate of approximately 50% at 1 year with 5% precision and 95% confidence intervals (CIs), 384 assessable patients per region/country were needed. With an expected lost-to-follow-up rate of 25%, approximately 6,100 patients were to be included to provide 4,600 assessable patients. Primary endpoints were therapeutic success and the presence of clinical outcome events. Secondary endpoints were assessment of AF control, proportion of patients in sinus rhythm, treatment modalities, and adverse reactions to AF treatments.

Statistical methods. Descriptive information is summarized as mean \pm SD and the number of nonmissing data for quantitative data. Categorical data are summarized as number and percentage of the population with nonmissing data. Baseline characteristics were compared between groups using a chi-square test (categorical variables), analysis of variance, and a Wilcoxon test (continuous variables). Data collection and statistical analyses were performed by an external contract research organization, Lincoln Pharmaceuticals Ltd. (Gujarat, India).

To identify factors associated with clinical outcomes and therapeutic success, univariate analyses were performed, with subgroup comparisons made by chi-square tests; multivariable stepwise logistic regressions were also performed on clinical outcomes, therapeutic success, and progression to permanent AF at 1 year, with a p value of 0.05 required for entering and retaining the variable in the model. Discrimination between models was assessed using c-statistics, and calibration was assessed using Hosmer-Lemeshow chi-square statistics. Odds ratios (ORs) and associated 95% CIs for therapeutic success, for having a clinical outcome, or for progression into permanent AF were determined. Multivariable analyses were adjusted for country.

The propensity score associated with the therapeutic strategy chosen at baseline was calculated; a stepwise logistic regression was used to estimate the score for each patient, and covariates were retained in the model if they were significant at the 0.50 level. Variables used to calculate the propensity score were age, sex, body mass index, country, AF classification (new diagnosis/paroxysmal/persistent), duration of AF (<3 months, ≥3 months), symptoms (at baseline or during the previous year), family history of AF, and history of MI, valvular heart disease, diabetes, dyslipidemia, carotid stenosis, heart failure (New York Heart Association functional class), and smoking status. Strata were created, defined by the quintiles of the propensity score. The effect of the strategy across strata was tested using the Mantel-Haenszel pooled estimate. The variables used in the models to predict outcomes, in addition to those used in the propensity score calculation, were a history of coronary artery disease (CAD), arterial hypertension, renal disease, stroke or TIA, and heart rate; the baseline status of AF was added for the analysis of progression into permanent AF.

A subset of patients at high risk of stroke and cardiovascular events was selected according to baseline characteristics: paroxysmal/persistent AF and age 75 years and older or 70 years and older with ≥1 risk factor: treated hypertension, diabetes, previous stroke/TIA, left ventricular ejection fraction ≤0.40. This population differed from the ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedaron 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death

from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter) trial population in that left atrial dimension was not a selection criterion, and symptom duration was limited to ≤12 months.

Analyses were performed with SAS statistical software, version 9.1 (SAS Institute, Cary, North Carolina).

Results

In total, 5,604 patients were eligible for analysis (Table 1), recruited from 532 sites in 21 countries across Europe, America, and Asia. The RECORDAF included areas reported to have a high burden of coronary heart disease (e.g., Eastern Europe, Russia, and Asia) (5), and differing antithrombotic use (6–9). Patient characteristics and AF management at baseline have been described previously (10).

Overall, patients assigned to a rhythm-control strategy were younger; more frequently symptomatic; more likely to have recently diagnosed AF, paroxysmal AF, or a history of lone AF; and had a lower resting heart rate compared with patients allocated to a rate-control strategy. A rate-control strategy was more often selected in patients with a history of heart failure, valvular heart disease, stroke, or diabetes, presenting with persistent AF, previous electrocardiographic evidence of AF, and the presence of AF at the inclusion visit. Most patients had a history of arterial hypertension (68%), and 42% had a history of dyslipidemia. **AF evolution.** At 1 year, 5,171 patients (92.3%) were assessable, with 81% of patients selected for a rhythm-control strategy remaining in sinus rhythm (44% at base-

Table 1 Baseline Characteristics in the RECORDAF Patients According to Treatment Strategy

Variable	Rhythm-Control Strategy	Rate-Control Strategy	Total	p Value
Age, yrs	64 ± 12.0 (n = 3,076)	67 ± 11.6 (n = 2,528)	66 ± 11.9 (N = 5,604)	<0.001 (A)
Sex				0.751 (C)
Male	1,755/3,076 (57.1)	1,453/2,528 (57.5)	3,208/5,604 (57.2)	
Race				<0.001 (C)
Caucasian	2,578/2,865 (90.0)	1,990/2,451 (81.2)	4,568/5,316 (85.9)	
Black	31/2,865 (1.1)	57/2,451 (2.3)	88/5,316 (1.7)	
Asian	167/2,865 (5.8)	352/2,451 (14.4)	519/5,316 (9.8)	
Other	89/2,865 (3.1)	52/2,451 (2.1)	141/5,316 (2.7)	
Resting heart rate, beats/min	76.6 ± 20.9 (n = 3,071)	80.6 ± 19.1 (n = 2,525)	78.4 ± 20.2 (n = 5,596)	<0.001 (W)
Atrial fibrillation on baseline ECG	1,172/3,047 (38.5)	2,007/2,494 (80.5)	3,179/5,541 (57.4)	<0.001 (C)
First AF diagnosis	180/3,076 (5.9)	120/2,528 (4.7)	300/5,604 (5.4)	0.050 (C)
Diagnosis in the previous year	2,863/3,076 (93.1)	2,391/2,528 (94.6)	5,254/5,604 (93.8)	
Paroxysmal AF	1,938/2,863 (67.7)	810/2,391 (33.9)	2,748/5,254 (52.3)	
Persistent AF	925/2,863 (32.3)	1,581/2,391 (66.1)	2,506/5,254 (47.7)	
Lone AF*	650/3,017 (21.5)	394/2,522 (15.6)	1,044/5,539 (18.7)	<0.001 (C)
Arrhythmia other than AF	425/3,015 (14.1)	293/2,480 (11.8)	718/5,495 (13.1)	0.013 (C)
Symptomatic AF (at the time of the visit or during previous year)	2,608/3,075 (84.8)	1,911/2,523 (75.7)	4,519/5,598 (80.7)	<0.001 (C)
Valvular heart disease	472/3,047 (15.5)	594/2,486 (23.9)	1,066/5,533 (19.3)	<0.001 (C)
Stroke	151/3,057 (4.9)	166/2,515 (6.6)	317/5,572 (5.7)	0.008 (C)
Heart failure	692/3,075 (22.5)	760/2,525 (30.1)	1,452/5,600 (25.9)	<0.001 (C)
History of diabetes	445/3,074 (14.5)	434/2,526 (17.2)	879/5,600 (15.7)	0.006 (C)

Values are mean ± SD or n/N (%).

A = analysis of variance; AF = atrial fibrillation; BMI = body mass index; C = chi-square test; ECG = electrocardiogram; W = Wilcoxon test.

Table 2 AF Status at 1 Year

	Rhythm-Control Strategy	Rate-Control Strategy	Total
Sinus rhythm*	2,247/2,791 (80.5)	712/2,147 (33.2)	2,959/4,938 (59.9)
AF	541/2,791 (19.4)	1,432/2,146 (66.7)	1,973/4,937 (40.0)
Paroxysmal AF	1,883/2,687 (70.1)	640/2,123 (30.1)	2,523/4,810 (52.5)
Persistent AF	447/2,687 (16.6)	340/2,123 (16.0)	787/4,810 (16.4)
Permanent AF†	357/2,687 (13.3)	1,143/2,123 (53.8)	1,500/4,810 (31.2)
Symptoms at the time of the visit‡	583/2,799 (20.8)	433/2,164 (20.0)	1,016/4,963 (20.5)

Values are n/N (%). *At baseline, 44% were in sinus rhythm, and 57% were in AF. †No permanent AF was found at baseline. ‡Forty-nine percent were symptomatic at the time of the baseline visit.
AF = atrial fibrillation.

line), whereas 67% of patients selected for a rate-control strategy were in AF (57% at baseline) (Table 2). The RECORDAF did not enroll permanent AF patients, but evolution to permanent AF occurred in 1,500 patients (31%) by visit 2 (rhythm control 13%; rate control 54%). Male patients made up 57% of those whose AF progressed to permanent.

Multivariable analysis demonstrated that presenting with a diagnosis of persistent AF, heart failure (New York Heart Association functional class I/II), a longer history of AF, and age older than 75 years predicted AF progression, whereas entering the study in sinus rhythm and the choice of rhythm control predicted that the arrhythmia would not progress (Fig. 1). When the propensity score was applied, the impact of the treatment strategy was as follows: OR: 0.20, 95% CI: 0.17 to 0.25; $p < 0.0001$.

Strategies, treatment, and adverse events. Overall, 52% of patients had a change in pharmacological treatment (rhythm control, 55%; rate control, 47%), 9% had a pharmacological conversion, and 10% had an electrical cardio-

version. Treatment using antiarrhythmic drug classes and rate-control agents was similar between baseline and visit 2 (class I antiarrhythmic drugs, 12% at both visits; class III antiarrhythmic drugs, 29% vs. 26%; heart rate-lowering calcium-channel blockers, 10% at both visits; cardiac glycosides, 20% at both visits). Two percent of rhythm-control patients had catheter ablation and 0.3% had surgical therapy for AF. Two percent of patients underwent a pacemaker implantation, 5% of patients had a new diagnosis of other arrhythmia (same in both strategies), but no cases of torsade de pointes were reported.

In total, 28% of patients had ≥ 1 treatment-related adverse events, mostly general side effects (13%) and mild electrocardiographic changes (9%) (Table 3).

At baseline, a rhythm-control strategy was selected in 55% of patients and a rate-control strategy in 45%. At 1 year, 78% of patients in each group remained on the same strategy.

Ninety percent of patients received antithrombotic therapy at 1 year, although only 52% were treated with a vitamin K

Persistent AF vs. paroxysmal AF
(3.31; 2.65 to 4.13; $p < 0.0001$)

Rhythm vs. rate control
(0.21; 0.17 to 0.25; $p < 0.0001$)

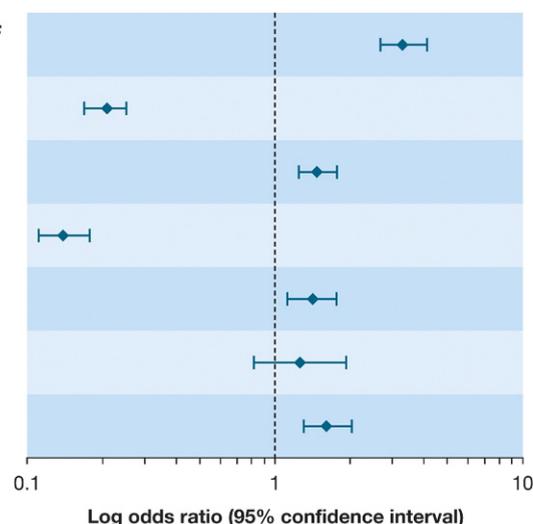
Duration of AF ≥ 3 m (yes vs. no)
(1.48; 1.24 to 1.79; $p = 0.0001$)

Sinus rhythm vs. AF
(0.14; 0.11 to 0.18; $p < 0.0001$)

NYHA class I/II vs. no HF
(1.41; 1.12 to 1.77; $p = 0.0033$)

NYHA class III/IV vs. no HF
(1.27; 0.82 to 1.94; $p = 0.2815$)

Age >75 y (yes vs. no)
(1.62; 1.30 to 2.04; $p < 0.0001$)

**Figure 1** Baseline Factors Predicting Progression to Permanent AF

Forest plot of multivariable analysis of baseline factors predicting progression to permanent atrial fibrillation (AF) (odds ratio, 95% confidence interval). c-statistics = 0.90, Hosmer-Lemeshow $p = 0.16$. HF = heart failure; NYHA = New York Heart Association.

Table 3 Adverse Events Occurring During the 1-Year Survey

Adverse Events	Rhythm-Control Strategy	Rate-Control Strategy	Total
Any adverse event	801/2,795 (28.6)	598/2,160 (27.4)	1,399/4,975 (28.1)
Gastrointestinal	161/2,782 (5.8)	126/2,164 (5.8)	287/4,946 (5.8)
Cardiac side effect	198/2,782 (7.1)	198/2,162 (9.2)	396/4,944 (8.0)
Heart failure	36/2,782 (1.3)	67/2,162 (3.1)	103/4,944 (2.1)
Electrocardiographic change	284/2,776 (10.2)	165/2,153 (7.6)	449/4,929 (9.1)
Sinus bradycardia	149/2,776 (5.4)	60/2,153 (2.8)	209/4,929 (4.2)
Organ toxicity	130/2,782 (4.7)	47/2,162 (2.2)	177/4,944 (3.6)
General side effect	343/2,791 (12.3)	310/2,165 (14.3)	653/4,956 (13.2)
Bleeding related to OAC	93/2,785 (3.3)	89/2,165 (4.1)	182/4,950 (3.7)

Values are n/N (%).
 OAC = oral anticoagulant.

antagonist, whereas 43% received aspirin and 6% had other antiplatelet agents; the mean (SD) duration of intake of vitamin K antagonists during the study was 10.8 (3.5) months. In 46% of patients, the CHADS₂ score was ≥2 at 1 year; 64 patients (1.3%) had an increased score compared with baseline. Fifty-nine percent of patients with a CHADS₂ score ≥2 (at baseline or 1 year) were treated with a vitamin K antagonist.

Endpoints. Clinical outcome events occurred in 18% of patients: 17% of patients when the strategy chosen at baseline was rhythm control and 18% when it was rate control (Table 4). Cardiovascular death occurred in 1.7% of patients (rhythm control, 0.9% vs. rate control, 2.8%), MI in 0.7% (0.5% vs. 0.9%), stroke/TIA in 2.1% (1.7% vs. 2.8%), and all-cause mortality in 3% (1.9% vs. 4.2%). Hospitalizations for cardiovascular reasons occurred in 16.7% of the population, and rates were similar for both treatment strategies (rhythm control 16.6%; rate control 16.7%).

Baseline factors significantly increasing the risk of clinical events in a univariate analysis were presence of symptoms at baseline/during the previous year; a history of CAD, MI, stroke/TIA, carotid stenosis, hypertension, heart failure, dyslipidemia, diabetes, valvular heart disease, arrhythmia other than AF, or the presence of renal disease; treatment

with antithrombotic drugs; and a CHADS₂ score ≥2. Baseline factors decreasing the risk of clinical events were lone AF and the absence of symptoms at baseline/during the previous year.

The multivariable model (Fig. 2) demonstrated that adverse clinical outcomes were predominantly influenced by history of heart failure (e.g., New York Heart Association functional class III to IV, OR: 2.03, 95% CI: 1.38 to 2.99) and higher heart rate (OR: 1.009 per 1-beat increase, 95% CI: 1.004 to 1.01), whereas a longer (≥3 months) duration of AF (OR: 0.82, 95% CI: 0.69 to 0.97) led to improved outcomes. The rhythm-control strategy did not affect clinical outcomes.

Control of AF, as defined here, was obtained in 78% of patients, whereas 22% had a strategy change between baseline and 1 year. The composite endpoint of therapeutic success was met in 54% of patients (rhythm control 60% vs. rate control 47%) (Table 5). Post-hoc analyses testing different cutoff values for resting heart rates were also performed: rates ≤85 beats/min demonstrated a better therapeutic success for the rhythm-control group compared with the rate-control group (60% vs. 52%, respectively, p < 0.0001); however, rates ≤90 beats/min neutralized therapeutic success (60% vs. 58%, p = 0.0652), as did rates ≤95

Table 4 Clinical Outcomes at 1 Year

Clinical Events	Rhythm-Control Strategy	Rate-Control Strategy	Total	p Value
Any clinical event	483/2,809 (17.2)	405/2,225 (18.2)	888/5,017 (17.7)	0.352
CV death	24/2,804 (0.9)	61/2,213 (2.8)	85/5,034 (1.7)	<0.001
Stroke or TIA	46/2,784 (1.7)	60/2,179 (2.8)	106/4,963 (2.1)	0.008
Myocardial infarction	14/2,785 (0.5)	20/2,175 (0.9)	34/4,960 (0.7)	0.078
Hospitalization or prolongation of hospitalization for arrhythmia or proarrhythmia	314/2,790 (11.3)	159/2,179 (7.3)	473/4,969 (9.5)	<0.001
Hospitalization or prolongation of hospitalization for other CV events or interventions	190/2,791 (6.8)	204/2,182 (9.3)	394/4,973 (7.9)	0.001
Congestive heart failure	67/2,791 (2.4)	104/2,182 (4.8)	171/4,973 (3.4)	<0.001
Unstable angina	35/2,791 (1.3)	33/2,182 (1.5)	68/4,973 (1.4)	0.436
Other	104/2,791 (3.7)	103/2,182 (4.7)	207/4,973 (4.2)	0.082
Hospitalization or prolongation of hospitalization for major complications of ablative procedure	15/2,786 (0.5)	14/2,171 (0.6)	29/4,957 (0.6)	0.626
Hospitalization for CV event: yes	465/2,793 (16.6)	366/2,195 (16.7)	831/4,988 (16.7)	0.891

Values are n/N (%).
 CV = cardiovascular; TIA = transient ischemic attack.

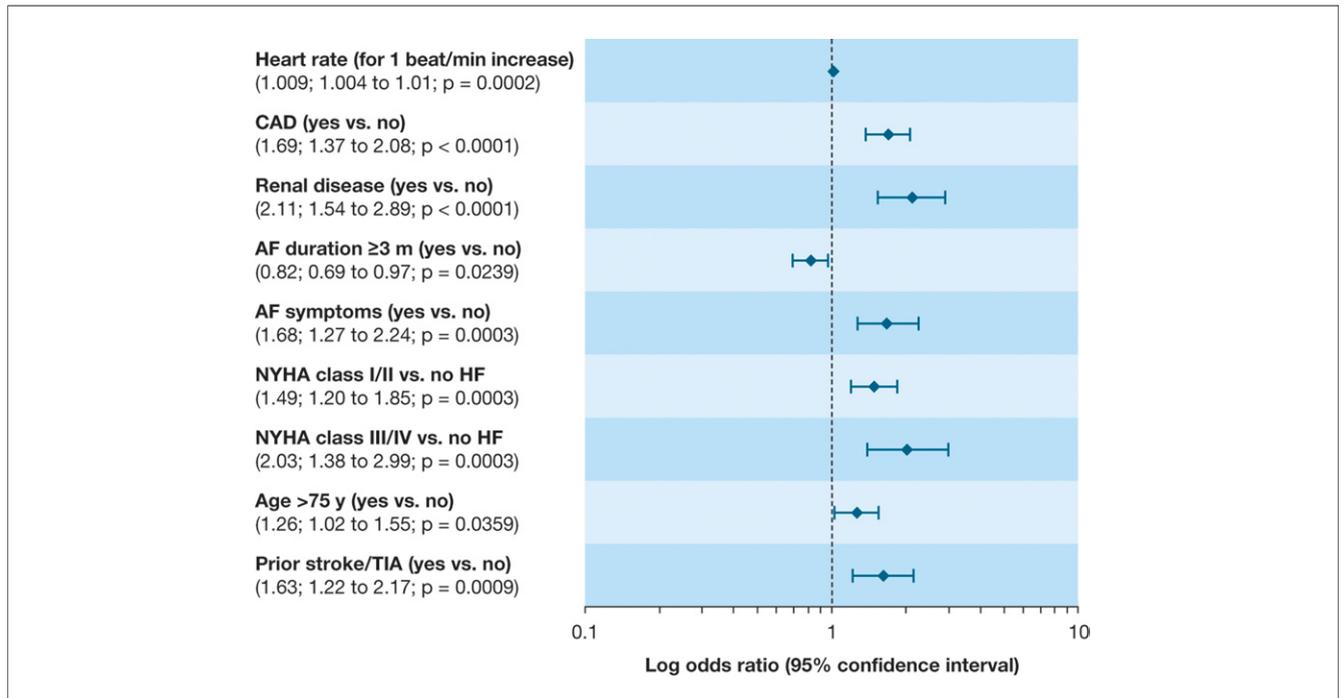


Figure 2 Baseline Factors Predicting Clinical Outcomes

Forest plot of multivariable analysis of baseline factors predicting clinical outcomes (odds ratio, 95% confidence interval). c-statistics = 0.67, Hosmer-Lemeshow p = 0.28. Abbreviations as in Figure 1.

beats/min (60% vs. 60%, p = 0.8903) and ≤100 beats/min (60% vs. 62%, p = 0.2842).

Baseline factors significantly increasing therapeutic success in the univariate analysis were age younger than 65 years, paroxysmal AF, lone AF, treatment with class I antiarrhythmic drug (vs. no class I), treatment with anti-thrombotic drugs, and choice of a rhythm-control strategy. Factors significantly decreasing success were persistent AF; a history of CAD, MI, stroke/TIA, carotid stenosis, heart failure, diabetes, or valvular heart disease; a CHADS₂ score ≥2; and choice of a rate-control strategy.

In a multivariable analysis, prognostic factors significantly increasing the chance of therapeutic success at 1 year, adjusted for baseline differences (Fig. 3) were rhythm-control strategy (OR: 1.67, 95% CI: 1.45 to 1.91; p < 0.0001), absence of CAD, absence of heart failure, age 75 years and younger, and no previous stroke/TIA (c-statistics = 0.62, Hosmer-Lemeshow p = 0.22). When the propensity score quintile was used, a higher therapeutic success rate was

still predicted for the rhythm-control strategy (OR: 1.34, 95% CI: 1.15 to 1.55; p = 0.0002).

In an analysis that included the composite CHADS₂ score rather than its constituent parameters, the statistical fit was less good (c-statistics = 0.62, Hosmer-Lemeshow p = 0.01). However, a CHADS₂ score ≥2 predicted a lower probability of therapeutic success (OR: 0.71, 95% CI: 0.62 to 0.81; p < 0.0001), and treatment strategy remained the most significant factor (OR: 1.71, 95% CI: 1.49 to 1.95; p < 0.0001).

Subgroup analysis. Among the 5,171 patients assessable at 1 year, 1,951 patients (38%) were at high risk of stroke and major cardiovascular events (i.e., they fulfilled the ATHENA trial [11] inclusion criteria [except time from AF diagnosis and left atrial dimension criteria]). Clinical outcomes occurred in 20% of patients in this subgroup: 21% when the baseline strategy was rhythm control, 19% when it was rate control. Cardiovascular death occurred in 2.2% of patients (1.4% vs. 3%). AF control was achieved in 76% of patients, whereas 24% underwent a strategy change between

Table 5 Therapeutic Success at 1 Year

	Rhythm Control	Rate Control	Total
Therapeutic success	1,691/2,814 (60.1)	1,026/2,208 (46.5)	2,717/5,022 (54.1)
Control of atrial fibrillation	2,247/2,791 (80.5)	1,561/2,122 (73.6)	3,808/4,913 (77.5)
Change in strategy between baseline and 1 year	618/2,796 (22.1)	497/2,182 (22.8)	1,115/4,978 (22.4)
No clinical outcome	2,326/2,809 (82.8)	1,820/2,225 (81.8)	4,146/5,034 (82.4)

Values are n/N (%).

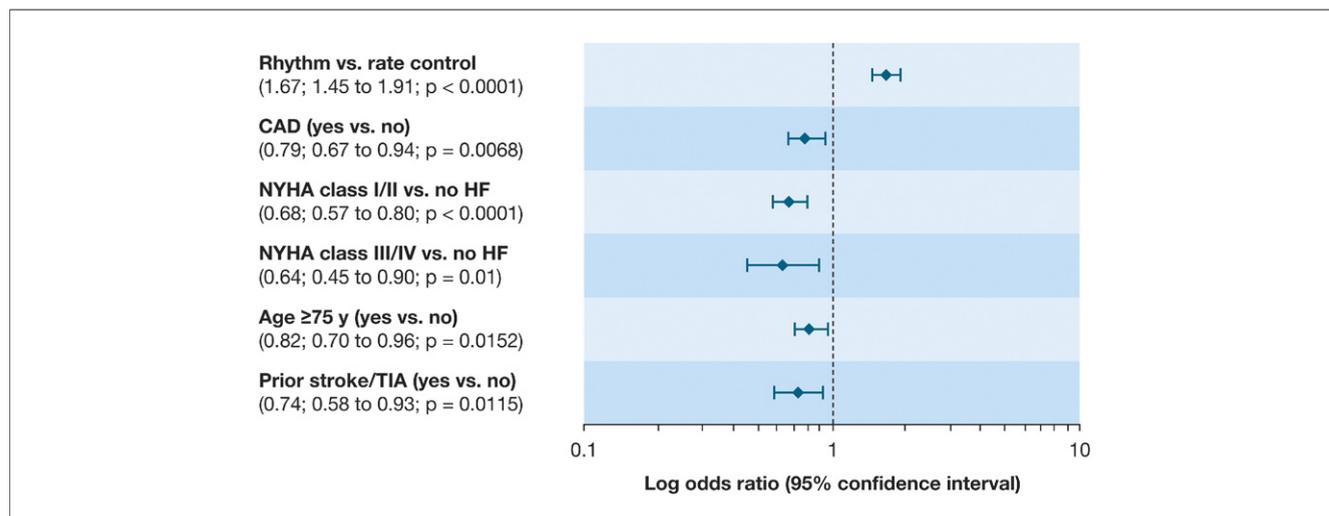


Figure 3 Baseline Factors Predicting Therapeutic Success

Forest plot of multivariable analysis of baseline factors predicting therapeutic success (odds ratio, 95% confidence interval). c-statistics = 0.62, Hosmer-Lemeshow p = 0.22. Abbreviations as in Figures 1 and 2.

baseline and 1 year; this is not different from the overall registry population. Therapeutic success was achieved in 51% of patients (rhythm control, 54%; rate control, 48%).

Discussion

RECORDAF. A large-scale longitudinal registry of AF patients treated according to clinical principles and practice offers an opportunity to seek information complementing that derived from randomized clinical trials. More than 5,000 patients were recruited to RECORDAF and followed for 1 year to statistically evaluate clinical outcomes and therapeutic success associated with rate-control and rhythm-control strategies in real life.

Clinical outcomes. Although clinical outcomes were documented in 18% of patients, there was no difference between strategies. Predictably, baseline characteristics forecasting adverse outcomes in multivariable analysis were renal disease, CAD, heart failure, previous stroke, and age. Furthermore, symptoms (recorded at baseline/during the previous year) predicted an adverse outcome independent of associated cardiovascular disease. It was hypothesized that symptoms may be more prominent in those with faster heart rates, but the statistical model demonstrated that heart rate had only a minor effect and that symptom effect was independent. However, it may be that symptoms drive hospitalizations or are a surrogate for unmeasured variables relating to greater illness severity.

A short duration of AF (<3 months) was associated with worse outcomes, consistent with the findings from the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) clinical study and the EUROHEART AF survey that new-onset AF has an adverse prognosis (11). Presumably, this is related to the adverse effect of the comor-

bidity that caused the AF to be discovered or precipitated the arrhythmia.

Although clinical outcome rates were not significantly different between treatment strategies, more serious events, including hospitalization for heart failure, occurred in patients receiving a rate-control strategy because these patients had a more severe risk profile than patients in the rhythm-control group. However, more hospitalizations for arrhythmias/proarrhythmias were observed in patients treated with a rhythm-control strategy.

Rate versus rhythm strategy. Despite considerable clinical trial data that led many physicians to conclude that AF is as well, if not better, managed with a rate-control strategy than with a rhythm-control strategy, the RECORDAF found that physicians generally prefer rhythm-control strategies. Cited reasons include the limitations of randomized trials, particularly the restricted nature of patient enrollment, and the clinical applicability of conclusions drawn from studies in which strategies are persistently applied despite their failure to control AF. Results from the largest of the rate-versus-rhythm trials (AFFIRM) indicate that patients who are in sinus rhythm, regardless of the strategy assignment, do better with regard to specific clinical outcomes, such as risk of death, than those who have AF (12). In this same trial, nearly 45% of screened candidates were not enrolled (1).

Subgroup analysis. The secondary analysis of a subset of patients with characteristics similar to those recruited in the ATHENA trial (13) did not reveal any substantial differences. Total clinical outcomes, cardiovascular death, and hospitalization for cardiovascular events were slightly, but not significantly, in favor of rhythm control. This population is of particular interest in view of the important decrease in hospitalizations and cardiovascular mortality in

such patients when treated with dronedarone (13), an antiarrhythmic drug recently approved in North America and the European Union for the management of AF with associated cardiovascular risk factors.

Therapeutic success. In the RECORDAF, therapeutic success at 1 year was achieved in 54% of patients (rhythm control, 60%; rate control, 47%), but approximately one-half of patients had changed their pharmacological AF treatment since baseline. Although the use of a single ECG as a measure of therapeutic success is quite limited, especially for patients with paroxysmal AF, the rhythm-control success rate (81%) established in the RECORDAF was almost identical to the overall success at maintaining sinus rhythm achieved in the first antiarrhythmic drug substudy of the AFFIRM study (14).

Moreover, the statistically significant higher therapeutic success associated with rhythm control in the multivariable analysis was largely due to the failure of therapy in the rate-control group to reduce heart rate to ≤ 80 beats/min. This heart rate was chosen in line with that in the AFFIRM study (1) and subsequent AF guidelines (15). Post hoc analyses using higher cutoff values for heart rate gave neutral results with regard to overall therapeutic success.

Adequate rate control: heart rate definition. The choice of a specific resting heart rate to define adequate rate control remains arbitrary. The American College of Cardiology/American Heart Association/European Society of Cardiology guidelines define adequate resting heart rate control as 60 to 80 beats/min. Although ≤ 80 beats/min was selected by the AFFIRM study investigators (1), a definition of ≤ 100 beats/min was chosen in the RACE (RATE Control Efficacy in permanent AF) trial (2). A subsequent comparison between outcomes in these trials failed to show any difference (16). Similarly, in the AFFIRM study, the clinical outlook was not improved for those meeting rate-control criteria compared with those who did not (17). However, data from the RACE II trial comparing strict and lenient rate control have now been published (18). Although the trial did not show any advantage from strict compared with lenient rate control, only relatively well patients were enrolled, the trial was small, and a large composite primary endpoint was used. In light of the important disadvantageous effect of faster rates during sinus rhythm (19–21), it is quite possible that a trial of sufficient size and duration in sick patients with AF and with a greater heart rate difference between lenient and strict rate-control arms would show a similar detrimental effect of higher heart rates in AF. Thus, 80 beats/min was chosen as the protocol definition of adequate rate control for the RECORDAF.

Progression to permanent AF. The 12-month follow-up in the RECORDAF showed a remarkable progression to permanent AF in patients treated with a rate-control strategy (none at baseline vs. 54% at 1 year). Because this classification was based on the investigators' clinical judgment, it may be that the observation is partly semantic, the choice of rate control implying that AF is permanent.

Alternatively, it may signal an important shift in attitude. When choosing rate control, physicians accept that AF will inevitably become permanent; conversely, only 13% of patients receiving rhythm-control therapy were subsequently designated as having permanent AF. Furthermore, there was a substantial difference between those who were documented to be in AF at visit 2 (rhythm control, 19% vs. rate control, 67%) compared with baseline (39% vs. 81%). These results may suggest an increased likelihood of the development of permanent AF if a rate-control strategy is chosen. Consequently, for any patient for whom a rhythm solution might later be chosen, there exists a clinical argument to persist with a rhythm-control strategy until definitive rhythm control can be offered.

It is generally believed that rate control is more simply and easily achieved than rhythm control (22). However, the results of the RECORDAF do not support this: a change of strategy, from rate control to rhythm control or vice versa, was similar in both groups. In addition to the failure of rate control to reach acceptable resting heart rates, 47% of patients required therapy adjustment (addition or exchange of rate-control medications) compared with 55% in the rhythm-control arm. Symptom resolution was identical in both groups, and similar frequencies of treatment-related adverse events were reported with both strategies.

Study limitations. A registry-based study has clear intrinsic limitations. Importantly, in this study, the rate- and rhythm-control groups were very different because the patients were not randomized to treatment assignment. Those who received rate-control therapy had worse underlying heart disease (e.g., only 16% of the rate-control group had lone AF compared with 19% of the rhythm-control group [$p < 0.001$]), and any valid comparison between the groups therefore relies on multivariable statistical analysis. The analyses in this study incorporated many variables that could be derived from history taking, but the patients were not extensively or consistently investigated with noninvasive or invasive techniques. The models successfully accounted for 62% (therapeutic success) and 67% (clinical outcomes) of the risk attributable to factors other than AF.

The registry included multiple countries, giving a global perspective, but including regional differences in clinical strategy, patient baseline variables, and recruitment setting (outpatient vs. inpatient). Individual country analysis may therefore be of value but, due to sample size, may not be powered to report statistical differences.

Success with the rhythm-control strategy was defined as sinus rhythm present at the 12-month visit. An ECG at a single point in time might represent an inadequate indication of the frequency of AF, and it is possible that patients with frequent AF who are in AF one-half of the time could be classified as having successful rhythm control in the RECORDAF. In this real-life observational registry, close monitoring of AF recurrences could not be achieved.

Success of rate control was defined per protocol as a resting heart rate ≤ 80 beats/min at the 12-month visit, but

resting heart rate assessment may be inadequate because an evaluation during activity or exertion is lacking.

The criteria for AF control were necessarily different for each strategy and, because they are arbitrary, the outcome of therapeutic success incorporating AF control should be interpreted with caution. Nevertheless, in clinical practice, AF control and therapeutic success are judged on a patient basis using similar pragmatic observations by which to infer the likely intermediate and longer-term outcome.

Therapeutic success also required that no change in therapeutic strategy (rate control vs. rhythm control) and that no clinical outcome as mentioned in the protocol had occurred. Therapeutic strategy and changes were determined by the treating physician, and it is likely that treatment varied by physician, region, or country.

Longitudinal registries are difficult to complete because patients and physicians may lose their enthusiasm for the study, but in this case, a majority of patients completed the 1-year follow-up (92%).

Conclusions

The RECORDAF, despite limitations inherent in real-life observational studies, has shown that within 12 months, clinical outcomes are not influenced by the choice of rhythm control versus rate control, but are mainly driven by hospitalizations due to arrhythmia/proarrhythmia and other cardiovascular causes. Nevertheless, AF is better controlled in clinical terms with a rhythm-control strategy, and the likelihood of progression to permanent AF is less with rhythm-control than with rate-control therapy. However, major cardiovascular outcomes are more dependent on comorbidity than the choice of cardiac rhythm management. The RECORDAF confirms and complements results reported in previous rate-control versus rhythm-control randomized, controlled trials.

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