ORIGINAL ARTICLE

Functional status with rhythm- versus rate-control strategy for persistent atrial fibrillation

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KEY WORDS

functional capacity, persistent atrial fibrillation, quality of life, treadmill test

ABSTRACT

INTRODUCTION Recent studies have shown that rhythm control does not provide additional benefit over rate control in terms of morbidity or mortality and is less cost effective in patients with atrial fibrillation (AF). It remains to be determined if any of the treatment strategies should be favored on the basis of the quality of life (QoL) or functional capacity.

OBJECTIVES This HOT CAFE substudy was conducted to compare the functional status of patients with persistent AF assigned either to rate or rhythm control strategy.

PATIENTS AND METHODS We enrolled 205 patients (mean [SD] age, 60.8 [11.2] years) with persistent AF who were randomly assigned either to rate or rhythm control strategies. The New York Heart Association (NYHA) functional classification, intensity of arrhythmia-related symptoms, exercise tolerance, and QoL were analyzed.

RESULTS After a mean (SD) of 1.7 (0.4) years, the NYHA class and QoL improved in both groups. Both strategies lead to improvement in AF-related symptoms. Treadmill test duration and maximal workload increased over time in both groups. In terms of NYHA class improvement, rhythm control was superior to rate control in patients with AF and hypertension (odds ratio [OR], 1.89; 95% CI, 0.98–3.65; $P = 0.055$) and in those with moderate HF (OR, 2.04; 95% CI, 1.03–4.06; $P = 0.04$). When success was considered as left ventricular function improvement, the rhythm-control strategy also proved to be superior in patients with hypertension (OR, 2.64; 95% CI, 1.21–5.74; $P = 0.01$) and those with NYHA class II or III (OR, 4.27; 95% CI, 1.25–9.85; $P < 0.001$).

CONCLUSIONS Rate- and rhythm-control strategies improved functional status in patients with persistent AF. However, rhythm control might be more appropriate for patients with AF and hypertension and those with moderate HF.

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INTRODUCTION Atrial fibrillation (AF) is the most prevalent sustained arrhythmia leading to hospital admission, as well as increased morbidity and mortality.[1] Most patients with AF report symptoms associated with this condition that can lead to a decrease in health-related quality of life (QoL) and functional status. There are several treatment strategies targeted at improving AF symptoms. The goals of these therapies are either to restore sinus rhythm (SR) or achieve rate control with medications and invasive cardiac procedures. Several studies have evaluated the effect of restoring SR or achieving adequate heart rate (HR) control on symptoms, and, generally, they have shown that improving rhythm does not alleviate symptoms.[2] Recent studies have demonstrated that rhythm control does not provide any benefit over rate control in terms of morbidity or

mortality and is less cost effective.[3,4] It remains to be determined whether any of these treatment strategies or the maintenance of SR should be favored on the basis of QoL or functional capacity. These important prespecified secondary outcomes constitute the focus of this a priori–defined substudy of the Polish HOT CAFE (How to Treat Chronic Atrial Fibrillation) trial.

PATIENTS AND METHODS The HOT CAFE substudy was conducted to compare the functional status of patients with persistent AF assigned either to rate-control (group 1) or rhythm-control (group 2) strategy. The study design, patient characteristics, and the primary results of the study were published previously.[5,6] In short, HOT CAFE was a prospective multicenter open-label randomized clinical trial designed to evaluate the effects of rhythm versus rate control in patients with mildly symptomatic nonvalvular persistent AF. The primary endpoint was a composite of death from any cause, thromboembolic complications, intracranial or other major hemorrhage, and invasive procedures for optimal ventricular rate control. Secondary endpoints included rate control, SR maintenance, discontinuation of therapy, hemorrhage, hospitalization, new or worsening congestive heart failure (HF), QoL, and changes in exercise tolerance. The parametrs of interest were compared between rhythm- and rate-control groups according to an intention-to-treat rule. The results of rate-control strategy were compared with the subgroups of rhythm control divided according to success in SR restoration and its long--term maintenance: patients who showed SR restoration or maintanance at the end of follow-up (group 2A); patients in whom SR was restored and maintained but who experienced AF relapse during subsequent follow-up (group 2B); and patients assigned to rhythm-control strategy in whom SR could not be restored (group 2C). The Bioethical Committee of the Medical University of Warsaw approved the study protocol and the informed consent form. The study was conducted in accordance with the current version of the Declaration of Helsinki at the time when the study was designed, and written informed consent was obtained from all participants.

Functional capacity assessment Functional capacity was assessed by standard indices, including the New York Heart Association (NYHA) functional classification to assess congestive HF symptoms (ie, dyspnea and fatigue), as well as by an exercise treadmill test (ETT). The NYHA class was assessed at baseline, and then at 1, 2, 3, 6, and 12-month follow-up visits. Exercise capacity was determined during symptom-limited ETT, according to the modified Bruce protocol. Heart rate during AF was determined by measuring the average HR for 15 seconds. Parameters such as maximal workload and exercise duration were included in further analysis. The ETT was performed in all study patients at baseline, prior to electrical cardioversion, 30 days after the procedure, and at 12-month follow-up, and was repeated as often as needed in the rate-control group to achieve optimal HR control.

Health-related quality of life Health-related QoL was determined using the Medical Outcomes Study Short-Form Health Survey (SF-36) questionnaire containing items for assessing both physical and mental health. Scores may range from 0 to 100, with higher values indicating better perceived QoL. Patients were instructed to complete the questionnaire at home at baseline and at 12-month follow-up. The SF-36 has been translated and validated in Poland.[7]

Statistical analysis Descriptive statistics were presented as frequency, arithmetic mean, and standard deviation for continuous variables and as number (percentage) for categorical variables. The repeated measures analysis of variance (ANOVA) was applied, considering the time, group, and the interaction of time and group effects, to assess changes in parameters characterizing the patient's clinical status and the results of echocardiography and exercise tests. Depending on ANOVA results, the differences between time points or between groups with respect to time points were evaluated using the paired and unpaired *t* test, respectively. The Bonferroni correction for multiple comparisons was used. Differences in the parameters of interest between the effects of rhythm control and cardioversion groups were assessed using 1-way ANOVA, followed by the Tukey multiple comparison test. Changes in the NYHA classification were assessed using the paired Wilcoxon test. Differences between groups at each visit were assessed using the Kruskal–Wallis test followed by the Mann–Whitney test, including the Bonferroni correction. Rhythm- and rate-control strategies in different subgroups of patients were compared using logistic regression and expressed as an odds ratio with 95% confidence interval and a *P* value. In all analyses, the statistical significance level was set at a *P* value of less than 0.05. S-Plus 2000 (MathSoft Inc., Seattle, Washington, United States) and SPSS 12.0 (SPSS Inc. Chicago, Illinois, United States) statistical packages were used in the analyses.

RESULTS In the HOT CAFE study, 205 patients at a mean (SD) age of 60.8 (11.2) years and mildly symptomatic nonvalvular AF were randomly assigned either to rate- or rhythm-control strategy. Patients were followed for a mean (SD) of 1.7 (0.4) years. The groups were similar in terms of baseline characteristics. None of the patients crossed over from one group to another during the study (TABLE 1).

A total of 101 patients were assigned to the rate--control strategy (group 1). The mean (SD) follow--up duration in this group was 1.6 (0.9) years, and none of the patients required cardioversion

TABLE 1 Baseline characteristics of the study groups

Variable		All patients (n = 205)	Rate-control strategy (n = 101)	Rhythm-control strategy (n = 104)	*P* value
Age, y, mean (SD)		60.8 (11.2)	61.4 (17.6)	60.4 (7.9)	0.73
Sex, female/male, n (%)		71 (34.6) / 134 (65.4)	38 (37.6) / 63 (62.4)	33 (31.7) / 71 (68.3)	0.46
AF duration, n (%)	7 days to 1 month	31 (15.1)	15 (14.9)	16 (15.4)	0.92
	1 month to 2 years	174 (84.9)	86 (85.1)	88 (84.6)	
AF duration, d, mean (SD)		231.3 (142.6)	243.2 (137.3)	220.4 (148.6)	0.25
History of paroxysmal AF, n (%)		79 (38.5)	42 (41.6)	37 (35.9)	0.38
Concomitant disease, n (%)					
Coronary heart disease		90 (43.9)	38 (37.6)	52 (50.0)	0.10
History of myocardial infarction		14 (6.8)	7 (6.9)	7 (6.7)	0.83
Coronary artery bypass grafting		1 (0.5)	0 (0.0)	1 (1.0)	0.99
Hypertension		132 (64.4)	60 (59.4)	72 (69.2)	0.19
Valvular heart disease		31 (15.1)	15 (14.8)	16 (15.4)	0.93
Idiopathic AF		43 (21.0)	25 (24.8)	18 (17.3)	0.26
Diabetes		33 (16.1)	18 (17.8)	15 (14.4)	0.64
Concomitant treatment, n (%)					
β-adrenolytics		172 (83.9)	90 (89.1)	82 (78.8)	–
Digoxin		60 (29.2)	43 (42.6)	17 (16.3)	–
Verapamil/diltiazem		15 (7.3)	8 (7.9)	7 (6.7)	–
ACEI		144 (70.2)	72 (71.2)	72 (69.2)	–
Amlodipine		28 (13.7)	13 (12.9)	15 (14.4)	–
Nitrates		18 (8.8)	9 (9.1)	9 (8.7)	–
Diuretics		31 (15.1)	16 (15.5)	15 (14.4)	–

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation

during follow-up. At the end of follow-up, AF was detected in all participants. A pacemaker was implanted in 1 patient in the rate-control group because of symptomatic slow ventricular rate or bradycardia; additional 2 patients required pacemaker implantation and atrioventricular node ablation. Rate-control therapy maintained ventricular response to AF within satisfactory ranges during follow-up (mean [SD], 86.2 [7.8] bpm vs 83.1 [4.3] bpm, $P = 0.09$).

SR restoration was attempted in all 104 patients in the rhythm-control group (group 2) and was successful in 90 patients (86.5%). The mean (SD) follow-up time was 1.8 (0.3) years. At the end of follow-up, there were 66 patients (73.3%) with confirmed SR. Two subjects (1.9%) in the rhythm-control arm required pacemaker placement due to bradycardia. Rhythm-control patients showed a continuous decline in HR frequency estimated by 24-hour Holter monitoring during follow-up. The mean HR measured 30 days after electrical cardioversion was lower compared with baseline (mean [SD], 96.0 [14.6] bpm vs 77.8 [17.0] bpm; $P < 0.001$). There were no other significant differences in the parameters during subsequent follow-up. A decrease in HR was observed only in group 2A (mean [SD], 97.2 [15.0] bpm at baseline vs 75.7 [14.1] bpm at 30 days; $P < 0.05$). During a mean (SD) follow-up of 1.7 (0.4) years, the mean (SD) HR in the rate-control arm was 85.8 (7.5) bpm, and in the rhythm-control arm, it was slightly lower: 79.1 (8.6) bpm ($P < 0.001$).

Left ventricular function In the rate-control group, a small, but in most patients systematic, reduction in left ventricular (LV) end-diastolic diameter (LVEDD) was observed during the 12-month follow-up (mean [SD], 50.8 [5.6] mm vs 50.0 [6.0] mm, $P = 0.045$). In the rhythm-control arm, there were no significant changes in the mean LVEDD during follow-up (mean [SD], 52.2 [6.8] mm vs 52.0 [7.4] mm). Moreover, there were no significant differences in the LVEDD between rhythm- and rate-control groups at any of the follow-up visits. Also, no differences were observed in the rhythm-control subgroups of patients.

Among rate-control patients, the difference in LV fractional shortening (LVFS) between baseline and 12-month follow-up were borderline significant (mean [SD], 32.8% [6.6%] vs 35.6% [7.4%], $P = 0.06$). The rhythm-control strategy led to an increase in the mean LVFS during the 12-month follow-up (mean [SD], 29.9% [6.9%] vs 34.5% [8.9%]; $P < 0.05$). However, a significant

TABLE 2 Changes in left ventricular echocardiographic parameters in the study groups during the 12-month follow-up

Parameter		Follow-up			*P* value		
		Baseline	2 months	12 months	Group	Time	Group × time interaction
LVEDD, mm	Rate control	50.8 (5.6)	50.9 (5.0)	50.0 (6.0)	0.03	<0.001	0.54
	Rhythm control	52.2 (6.8)	53.4 (5.5)	52.0 (7.4)			
FS, %	Rate control	32.8 (6.6)	32.8 (6.7)	35.6 (7.4)	0.61	<0.001	0.001
	Rhythm control	29.9 (6.9)	33.3 (8.2)	34.5 (8.9)			

Data are presented as mean (SD).

Abbreviations: FS, fractional shortening; LVEDD, left ventricular end-diastolic diameter

TABLE 3 Changes in left ventricular echocardiographic parameters in the rate-control group and rhythm-control subgroups

Parameter		Follow-up			*P* value		
		Baseline	2 months	12 months	Group	Time	Group × time interaction
LVEDD, mm	Group 1	50.8 (5.6)	50.9 (5.7)	50.0 (6.0)	0.92	0.18	0.78
	Group 2A	51.5 (7.2)	52.9 (5.9)	51.4 (8.4)			
	Group 2B	52.4 (5.3)	53.8 (4.2)	52.2 (4.8)			
	Group 2C	55.3 (5.9)	54.7 (5.6)	54.8 (5.1)			
FS, %	Group 1	32.8 (6.6)	32.8 (6.7)	35.6 (7.4)	0.001	0.001	0.002
	Group 2A	29.9 (7.6)	33.7 (5.6)	35.6 (9.3)			
	Group 2B	30.1 (6.4)	31.2 (6.4)	31.3 (7.3)			
	Group 2C	29.5 (4.0)	34.0 (9.4)	34.3 (8.5)			

Data are presented as mean (SD).

Goup 1, rate-control group; group 2A, patients with sinus rhythm (SR) restoration at 12-months; group 2B, patients assigned to SR restoration and maintenance who experienced AF relapse during follow-up; group 2C, patients assigned to rhythm-control strategy in whom SR could not be restored

Abbreviations: see TABLE 2

TABLE 4 Changes in maximal workload and exercise treadmill test duration in the study groups during the 12-month follow-up

Parameter		Follow-up			*P* value		
		Baseline	2 months	12 months	Group	Time	Group × time interaction
Maximal workload, METs	Rate control	5.3 (11.5)	4.5 (2.3)	4.8 (2.5)	<0.001	0.53	0.04
	Rhythm control	5.2 (5.1)	7.8 (2.9)	7.6 (3.3)			
ETT duration, s	Rate control	118.0 (87.5)	143.3 (123.3)	157.8 (126.2)	<0.001	<0.001	<0.001
	Rhythm control	125.3 (115.5)	301.7 (188.3)	294.7 (216.7)			

Data are presented as mean (SD).

Abbreviations: ETT, exercise treadmill test; MET, metabolic equivalent

increase was observed only in group 2A (mean [SD], 29.9 [7.6] vs 35.6 [9.3]%; P <0.05). No such changes were observed for group 2B or 2C. There were no significant differences in the mean LVFS at 12 months between rate- and rhythm-control groups (mean [SD], 35.6% [7.4%] and 35.6% [9.3%], respectively; TABLES 2 and 3).

Treadmill test Improvement of functional capacity over time was observed for both treatment strategies. The rhythm-control strategy resulted in an increase in the mean treadmill test duration as well as maximal workload during the study (mean [SD], 125.3 [115.5] s vs 294.7 [216.7] s and 5.2 [5.1] metabolic equivalents [METs] vs 7.6 [3.3] METs, respectively; P <0.05). This trend was observed only in group 2A. Patients in the rate-control group showed an increase in exercise duration during the 12-month follow-up (mean [SD], 118.0 [87.5] s vs 157.8 [126.2] s; P <0.05). Maximal workload was maintained at the same level during follow-up (mean [SD], 5.3 [11.5] METs vs 4.8 [2.5] METs; P = 0.42). At 12 months, exercise capacity assessed by maximal workload during the ETT was improved in the whole rhythm-control group and in subgroup 2A compared with patients with persistent AF (mean [SD], 8.5 [3.0] METs and 7.6 [3.3] METs vs 4.8 [2.5] METs; P <0.05 for both comparisons) (TABLES 4 and 5).

TABLE 5 Changes in maximal workload and treadmill test duration during the 12-month follow-up in the rate-control group and rhythm-control subgroups

Parameter		Follow-up			*P* value		
Baseline		2 months	12 months		Group	Time	Group × time interaction
Maximal workload, METs	Group 1	5.3 (11.5)	4.5 (2.3)	4.8 (2.5)	0.001	0.64	<0.001
	Group 2A	4.7 (2.3)	8.3 (2.7)	8.5 (3.0)			
	Group 2B	4.4 (2.2)	6.9 (2.7)	4.7 (2.7)			
	Group 2C	8.9 (2.2)	6.6 (3.1)	7.4 (2.7)			
ETT duration, s	Group 1	118.0 (87.5)	143.3 (123.3)	157.8 (126.2)	<0.001	<0.001	<0.001
	Group 2A	123.7 (108.1)	328.6 (195.2)	341.5 (208.0)			
	Group 2B	108.6 (105.2)	258.0 (160.3)	133.5 (128.5)			
	Group 2C	164.8 (137.7)	233.4 (174.5)	284.8 (231.5)			

Data are presented as mean (SD).

For description of groups 1, 2A, 2B, and 2C, see TABLE 4

Abbreviations: see TABLES 3 and 4

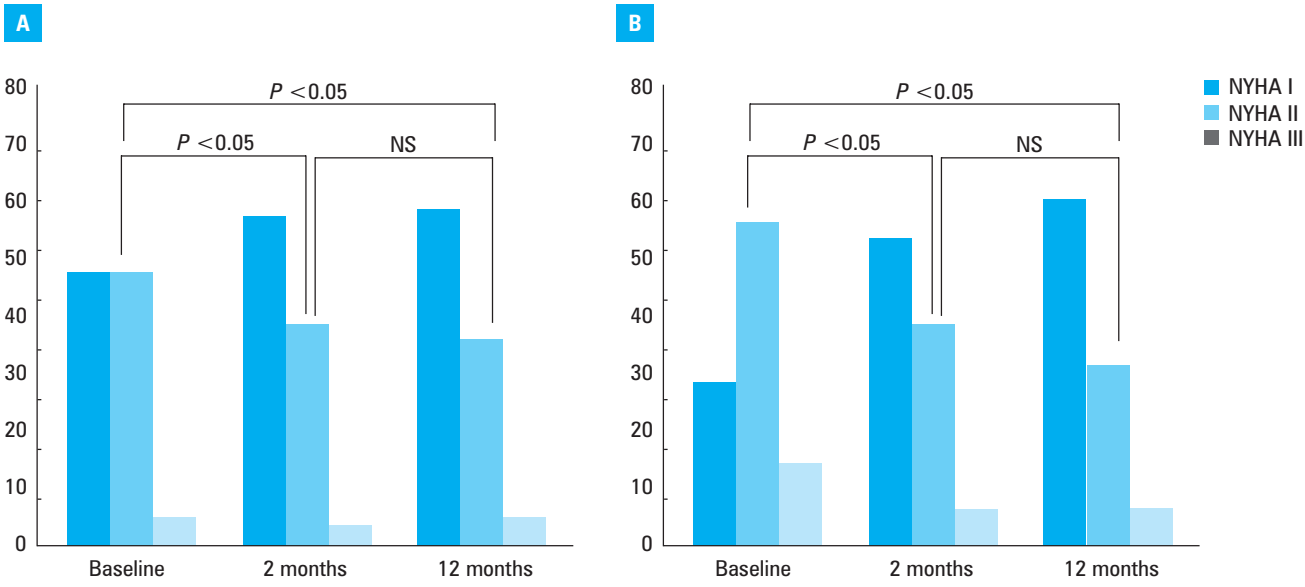

FIGURE 1 Changes in the intensity of heart failure symptoms assessed according to the New York Heart Association (NYHA) functional class during the 12-month follow-up in patients randomized to rate-control strategy (A) or rhythm-control strategy (B)
Abbreviations: NS, nonsignificant

New York Heart Association functional capacity The NYHA class improved during the 12-month follow-up in both arms (P <0.05). No significant differences between groups were observed in the NYHA class at baseline or during follow-up. Although the NYHA class improved over the 12-month follow-up in rhythm-control patients, this trend was observed only in subgroup 2A (P <0.05). In both groups, the greatest improvement in the NYHA class was observed during the first 2 months. Data are shown in FIGURE 1.

Health-related quality of life An improvement in the total QoL score was observed during follow-up both in the rhythm-control (by 22.3 points; P = 0.002) and rate-control (by 20.7 points; P = 0.003) arms. Both strategies resulted in an improvement in mental symptoms (rhythm control, by 5.9 points, P = 0.05; rate control, by 8.4 points, P = 0.003) and physical symptoms (rhythm control, by 13.9 points, P = 0.003; rate control, by 14.8 points, P = 0.001). The rhythm-control strategy resulted in a significant improvement in 5 of the 8 domains, and the rate-control strategy, in 6 of the 8 domains, of the SF-36 during the 12-month follow-up. In the rhythm-control group, only group 2A showed improvement in the QoL in comparison with the rate-control group. Data are shown in TABLES 6 and 7.

Functional status and rhythm- or rate-control strategies The outcomes of each of the strategies were compared according to patient age and sex, comorbidities, NYHA class, AF duration, history of paroxysmal arrhythmia, echocardiographic parameters, and ETT results. The impact of each

TABLE 6 Changes in the global quality of life score assessed using the SF-36 questionnaire in all patients and in individual study groups during the 12-month follow-up

Global quality of life score	Baseline	12-month follow-up	Change, Δ	*P* value
All patients	23.0 (19.4)	44.3 (35.2)	21.3 (48.2)	0.001
Rate control	23.3 (44.5)	43.8 (36.3)	20.7 (52.2)	0.003
Rhythm control	22.8 (37.1)	45.1 (33.8)	22.3 (41.9)	0.002
P value	0.96	0.86	0.86	–

Data are presented as mean (SD).

TABLE 7 Changes in the quality of life score (mental and physical characteristics) in all patients and in individual study groups during the 12-month follow-up

Quality of life		Baseline	12-month follow--up	Change, Δ	*P* value
Mental characteristics	All patients	27.8 (16.6)	34.7 (13.0)	6.9 (21.2)	0.001
	Rate control	27.0 (17.5)	32.9 (14.6)	5.9 (23.7)	0.05
	Rhythm control	29.2 (15.2)	37.6 (10.4)	8.4 (16.8)	0.003
	P value	0.49	0.91	0.53	–
Physical characteristics	All patients	49.2 (28.0)	65.3 (25.0)	16.1 (29.9)	0.001
	Rate control	49.9 (29.9)	64.9 (24.6)	15.0 (31.1)	0.001
	Rhythm control	48.0 (25.2)	65.9 (25.9)	17.9 (28.5)	0.003
	P value	0.73	0.85	0.88	–

Data are presented as mean (SD).

strategy was assessed on the basis of the improvement in the NYHA class or no deterioration for patients in NYHA class I, or the improvement in LV systolic function as assessed by the LVFS. Using the improvement in NYHA class as the criterion for a successful therapy, rhythm control was superior to rate control in patients with AF and hypertension (odds ratio [OR], 1.89; 95% CI, 0.98–3.65; $P = 0.055$ [borderline significance]) and in those with AF and moderate HF (OR, 2.04; 95% CI, 1.03–4.06; $P = 0.04$). Using the improvement in LV systolic function as the criterion, the rhythm-control strategy also proved superior to rate control in patients with hypertension (OR, 2.64; 95% CI, 1.21–5.74; $P = 0.01$), as well as in those in NYHA class II or III (OR, 4.27; 95% CI, 1.25–9.85; $P < 0.001$). There were no differences between strategies for the remaining parameters.

DISCUSSION Physical activity in patients with AF leads to a rapid increase in HR, which is an inadequate response to the effort in comparison with a linear increase in HR in patients with SR.[8-10] After SR restoration, the HR is slower both at rest and during exercise compared with AF. Restoration of SR is the preferred therapeutic strategy because it results in improved exercise tolerance and reduction in HF symptoms as assessed by the NYHA classification.[11-15]

The SAFE-T study (Sotalol-Amiodarone Atrial Fibrillation Efficacy Trial) has confirmed that restoration and maintenance of SR improves physical efficiency and exercise tolerance in patients with AF.[16] The CTAF study (Canadian Trial of Atrial Fibrillation) reported similar findings.[17] A moderate improvement in exercise tolerance was found only in patients with maintained SR at the end of the study. In patients with recurrence and intensification of arrhythmia, a significant change in physical efficiency was not observed. In the PIAF study, a significant improvement in exercise tolerance in the rate-control group during 12-month follow--up was reported.[18] An attempt to restore and maintain SR led to improved physical efficiency, as assessed by the 6MWT. Both rate- and rhythm-control groups showed a comparable decrease in symptom intensity associated with AF (76% and 70%, respectively, $P < 0.32$). The study did not find significant differences between the groups in terms of worsening of HF or symptoms of coronary heart disease. Similarly, the STAF study (Strategies of Treatment of Atrial Fibrillation) reported no difference in cardiac dynamics or worsening symptoms associated with arrhythmia between the rate- and rhythm-control groups.[19] None of the strategies were shown to impact functional capacity as assessed by the NYHA class. Similar findings were revealed in the AFFIRM study (Atrial Fibrillation Follow-up Investigation of Rhythm Management).[9,20] The authors reported that rhythm--control strategy did not result in a reduction in mortality, the number of strokes, or improved exercise tolerance. There were no significant differences in functional capacity and symptom intensity as evaluated by the NYHA class between

strategies. The PAF2 study (Paroxysmal Atrial Fibrillation 2) compared rhythm- and rate-control strategies in symptomatic patients with paroxysmal AF who were eligible for atrioventricular junction ablation and permanent pacemaker implantation or pharmacological treatment with antiarrhythmic agents.[11] Although the results did not show either strategy to be more beneficial in terms of QoL, symptom worsening, or echocardiographic parameters, the rate-control strategy was associated with a lower risk of HF development or progression. The benefit of the restoration and maintenance of SR compared with rate control in terms of QoL and improved exercise tolerance was shown in the CRAAFT trial (Cryoablation versus Radiofrequency Ablation in the treatment of Atrial Flutter).[21] However, the study protocol significantly differed from those discussed above. Patients who were enrolled in the CRAAFT trial had AF and rheumatic heart disease, and most of them underwent surgical correction of arrhythmia. The rhythm-control group consisted of comparatively young patients with a relatively low risk of arrhythmia recurrence, and all of them maintained SR during follow-up.

In the AIRCRAFT study (Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial), atrioventricular junction ablation was compared with pharmacological treatment in mildly symptomatic patients with AF.[13] Ablation did not worsen cardiac function. In the rhythm-control group, an improvement in LV ejection fraction (LVEF) and exercise tolerance was demonstrated. LV function during exercise was similar in both groups at the end of follow-up.

The AF-CHF trial (Atrial Fibrillation and Congestive Heart Failure), including 1376 patients with NYHA class II to IV, LVEF of 35% or lower, and AF episodes, reported no advantage of rhythm- over rate-control strategy.[22] During the 2-year follow-up, an intention-to-treat analysis did not demonstrate a significant difference in mortality between the groups. The total number of strokes and cases of HF worsening requiring hospitalization was similar in both groups. A subanalysis of the AF-CHF study reported that both strategies resulted in a similar improvement in QoL and 6MWT distance. The longer period of SR maintenance was associated with a greater improvement in the NYHA class (P <0.001) but not in the 6MWT (P = 0.14).[23]

In a recent meta-analysis, Sethi et al[24] reported that rhythm-control strategy was associated with an improvement in the physical scale of QoL as evaluated by the SF-36 (mean difference, 6.93 points; 95% CI, 2.25–11.61; P = 0.004). Similarly, the rhythm-control strategy demonstrated a significant increase in LVEF (mean difference, 4.2%; 95% CI, 0.54–7.87; P = 0.02). The trial sequential analysis (TSA) reported insufficient data to confirm or reject a mean difference of 4.20% (TSA-adjusted CI, –2.37 to 10.77).[24]

The results of the above trials are in line with our current findings. Both the rhythm- and rate-control strategies resulted in improved exercise tolerance during the 12-month follow-up. Maximal effort and exercise duration were significantly higher in the rhythm-control group at the end of the study. The beneficial effects were observed only in patients with maintained SR at 12 months. A significant improvement in exercise tolerance, as assessed by exercise electrocardiography, was observed in the first month after cardioversion. Further follow-up did not confirm significant changes in these parameters. In the rhythm-control group, in patients who continued to have arrhythmia or in whom SR was not maintained, a change in exercise tolerance during follow-up was not confirmed. The rhythm-control strategy resulted in improved functional capacity, as assessed by the NYHA class, during follow-up. In the rhythm-control group, reduction in the severity of HF symptoms was confirmed during the initial study period. Similarly to exercise tolerance, changes were observed only in patients who maintained SR. Compared with baseline values, remote observation of the rhythm-control group showed no significant differences in the NYHA class. Assuming the reduction of symptom severity as the criterion of procedural success, treatment to restore and maintain SR appeared to be more beneficial in patients with arterial hypertension and patients with NYHA class II or III. Similar results were obtained in the RACE study (RAte Control versus Electrical cardioversion).[25] In patients with moderate HF (NYHA class II and III), the restoration and maintenance of SR resulted in improved cardiac function and a reduction of symptoms requiring hospitalization.

Our study showed no clear benefit of rhythm control over rate control in terms of improved cardiac function in patients with AF. This finding is in line with previous studies.[9,18,19,25] Optimal HR control improves exercise tolerance and functional capacity. The lack of this clinical effect in the rate-control group after the 12-month follow-up may be explained by a less strict approach of attending physicians to controlling ventricular HR in patients with AF in routine outpatient care. This hypothesis could explain the deterioration of cardiac function in the rhythm-control group. It might have been challenging to change treatment at 12 months to ensure optimal rate control in patients with permanent arrhythmia that was worsening over time. The AFFIRM study demonstrated that implementing the rate-control strategy required frequent changes of drug classes and combination therapy, with predicted outcomes achieved only in approximately two thirds of patients.[26] Achievement of optimal results requires time and involvement of physicians, as well as numerous repeated tests and examinations. However, the 6MWT, 24-hour Holter monitoring, or resting HR measurement, all of which evaluate the effectiveness

of the rate-control strategy, are rarely performed in routine practice.

In the AFFIRM, PIAF, RACE, and STAF studies, as well as in our present study, both rhythm- and rate-control strategies resulted in improved functional capacity, exercise tolerance, and a reduction in HF symptoms.[9,18,19,25] In all cases, HR reduction at rest and during moderate exercise was satisfactory, although one report applied different criteria for optimal control of ventricular rhythm, yielding discrepant results. The subanalysis of the AFFIRM study confirmed that restrictive rhythm control did not improve incident-free period (P = 0.81), mortality (P = 0.13), or QoL in patients with AF.[26] In all cases, pharmacological treatment had a positive effect on physical efficiency and functional capacity. Therefore, it seems that prevention of uncontrolled tachycardia, inadequate and rapid changes in heart rhythm, and inadequate chronotropic response to exercise may have fundamental significance for treatment response, and strict rate control does not have to be the best therapeutic option.

In conclusion, our study confirms that functional status gradually improves over time in patients with AF treated with either rhythm- or rate--control strategy. The success rate for rhythm--control strategy is at least as good as for rate control, but only in patients who maintain SR in long-term follow-up. Although the rhythm--control approach to AF treatment is associated with higher hospitalization rates and side effects mainly due antiarrhythmic therapy, this strategy might be appropriate for patients with AF and concomitant hypertension or moderate HF. Moreover, our study shows that AF treatment may be guided by the underlying heart disease.

SUPPLEMENTARY MATERIAL Supplementary material is available with the article at www.pamw.pl.

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CONTRIBUTION STATEMENT GO, DK, DR conceived the concept of the study and contributed to the design of the research. GO, DK, MS was involved in data collection. All authors analyzed the data. All authors prepared, edited and approved the final version of the manuscript.

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