EDITORIAL

Improving symptoms and functional capacity in patients with atrial fibrillation: rate-control vs rhythm-control strategy

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Owing to its growing global prevalence and incidence among adults and a strong association with cardiovascular morbidity and mortality, atrial fibrillation (AF) imposes a significant burden on health care systems worldwide. Adequate thromboprophylaxis using oral anticoagulant therapy to reduce the risk of stroke and mortality, as well as aggressive control of associated cardiometabolic and lifestyle risk factors to reduce AF burden and further improve outcomes, are the cornerstones of a holistic approach to the management of AF patients, as summarized in the Atrial fibrillation Better Care (ABC) pathway for integrated management of AF patients (A—avoid stroke using oral anticoagulation, B—better symptom control using rate- or rhythm-control strategy, and C—cardiovascular risk factor/comorbidity management). The use of ABC pathway has been associated with a reduced risk of adverse outcomes (ie, mortality, stroke/major bleeding/cardiovascular death, and hospitalization) among AF patients.[1]

The third cornerstone of the integrated management of AF patients—better symptom control (the B component of the ABC pathway) using rate or rhythm control—addresses the risks associated with hemodynamic alterations caused by irregular and often fast ventricular rate in AF (ie, exacerbation of pre-existing or new-onset heart failure [HF], pronounced symptoms, impaired functional status, and overall decrease in the quality of life [QoL]).[1]

In many AF patients, an adequate ventricular rate control effectively prevents new onset or exacerbation of HF and alleviates symptoms related to fast ventricular rate.[2] In those with persisting symptoms despite rate control, rhythm-control strategy, including cardioversion and long-term use of antiarrhythmic drugs (AADs), catheter ablation (CA), and/or AF surgery for sinus rhythm restoration and maintenance, can be attempted.[3] Since AF is an evolving disease, and the use of AADs, CA, or AF surgery is associated with limited success, potentially serious complications, multiple hospitalizations, and high costs, it is important to assess realistically the anticipated long-term clinical benefits of rhythm control in each AF patient.[3]

Approximately 3 in every 4 patients with AF would experience some arrhythmia-related symptoms, most commonly palpitations.[4] Perception of symptoms is highly individual and symptom severity can vary substantially among different patients or in the same patient at different time points.[5] Elderly patients usually have less pronounced symptoms compared with younger patients, and those with paroxysmal AF have more severe symptoms requiring hospital admissions than patients with persistent or permanent AF. In the latter, symptoms often subside with longer duration of AF, especially after starting with the rate-controlling drugs.[2] Symptomatic patients more commonly have significant structural heart disease than those who are symptom free.[4]

Symptoms usually aggravate during physical activity, thus considerably limiting exercise capacity and functional status in more than 50% of AF patients.[3] It has been shown that the presence of sustained AF was associated with a significant reduction in exercise performance (15%–20%) in patients without structural heart disease, those with hypertension, and those with HF.[4,6] Importantly, successful rhythm control resulted in modest but significant improvement of peak O_2 uptake at cardiopulmonary exercise testing a month after cardioversion.[7] The presence of other cardiopulmonary comorbidities (eg, uncontrolled hypertension, coronary artery disease, and chronic lung disease), smoking, obesity, advanced age, and stroke-related disability may contribute considerably to further functional status decline in AF patients.[4]

In this issue of *Polish Archives of Internal Medicine*, Kosior et al[8] reported an ancillary analysis of the HOT CAFE study (How to Treat Chronic Atrial Fibrillation), evaluating functional status improvement in 205 patients with persistent AF, who were randomly assigned to pharmacological rhythm- (n = 104) or rate-control (n = 101) strategy. Since HOT CAFE was conducted almost 15 years ago, contemporary strategies for AF treatment (ie, CA procedures) were not available, which could significantly influence the study results because rhythm control in AF using AADs is inferior to CA with regards to the long-term rhythm outcome.[3] Nevertheless, the study provided very important information on the beneficial effects of rhythm-control strategy on functional status improvement in patients with persistent AF. During a mean follow-up of 1.7 years, the average heart rate was significantly lower with rhythm control than with rate control in the HOT CAFE cohort, and 73.3% of patients in the rhythm-control arm remained in sinus rhythm. At the end of follow-up, QoL, New York Heart Association (NYHA) functional class, and exercise capacity all improved in both treatment arms, but maximal workload at treadmill test and left ventricular (LV) fractional shortening were significantly better in the rhythm-control arm, especially in patients who remained in stable sinus rhythm during the study, with the greatest benefit from stable sinus rhythm observed in patients with hypertension and mild to moderate HF.

Previous randomized clinical trials reported no mortality or stroke benefit with pharmacological rhythm-control compared with rate-control strategy among AF patients,[2] whereas the findings pertinent to symptomatic and functional improvement were conflicting (TABLE 1).[2,9,10] Some studies (STAF [Strategies of Treatment of Atrial Fibrillation], AF-CHF [Atrial Fibrillation and Congestive Heart Failure], CAFE II [Controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure II]) reported no difference in functional status outcomes between the 2 strategies, while other studies (PIAF [Pharmacological Intervention in Atrial Fibrillation], AFFIRM [Atrial Fibrillation Follow-up Investigation of Rhythm Management], HOT CAFE [How to Treat Chronic Atrial Fibrillation], and CRAFT [Control of Rate vs Rhythm in rheumatic Atrial Fibrillation Trial])[2,11] showed better exercise tolerance with successful rhythm control, especially in HF patients (TABLE 1). Moreover, both the lenient and strict rate control led to similar functional performance recovery in patients with permanent AF.[2]

Contemporary evidence clearly shows the benefits of AF ablation over medical therapy in terms of functional status outcome, particularly in patients with symptomatic HF (TABLE 1).[12-14] In the recent CASTLE-AF study (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation),[13] patients with systolic LV dysfunction (ejection fraction <35%) who underwent CA of drug-refractory AF had lower AF burden, mortality, and HF progression rates and better exercise tolerance than those on medical therapy for AF.[14] In the CAMERA-MRI trial (Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction), CA of AF provided additional improvement of cardiac function and functional status compared with continued drug treatment in HF patients with optimal medical rate control.[12] A meta-analysis of 4 randomized studies[13] including AF patients with congestive HF showed CA of AF to be superior to rate control in improving LV systolic function and exercise capacity (TABLE 1). Even in asymptomatic patients with long-standing persistent AF, CA of AF led to significant long-term improvement in exercise tolerance.[15]

Of note, many essentially asymptomatic patients with permanent AF with acceptable rate control still would strongly prefer to be in normal sinus rhythm.[16] Reliable measurement of functional status in AF patients would facilitate clinical decision making on an optimal long-term treatment strategy (rate control vs rhythm control) and objective assessment of treatment effects. Several tests are available for the functional status evaluation in patients with AF.[4] Cardiovascular functional deterioration in an AF patient can be assessed by several simple (but subjective) clinical scales such as NYHA classification, European Heart Rhythm Association symptom score, Canadian Cardiovascular Society classification, the Specific Activity Scale, and the Duke Activity Status Index, all showing only modest reproducibility (50%–70%) due to self-reporting of symptoms and variable patient mental status and education.[4] Most of these scales provide insights only into a usual daily activity performance and not the maximal functional capacity during higher levels of physical activity,[4] whereas the 6-minute walk test, treadmill or bicycle exercise test (ergometry), and cardiorespiratory exercise test (spiroergometry) enable a more objective assessment of functional capacity.[4] Although these tests are highly reproducible and yield important information on the maximal exercise endurance and workload (eg, heart rate and blood pressure response to exercise, maximum oxygen uptake, and maximum exercise time), they are expensive and time consuming, and require patient's physical capability to perform testing.[4,15] These tests are proposed for assessing the overall cardiovascular functional status, but they cannot discriminate between functional deterioration attributable to AF and that resulting from other cardiovascular comorbidities, medical therapy, or physical disability, and only a weak correlation among postinterventional changes in functional

TABLE 1 Randomized studies comparing the effects of rate- and rhythm-control strategies on symptomatic and functional status in atrial fibrillation patients (continued on the next page)

Study	Participants	Rate control	Rhythm control	Functional status test	Mean follow-up, y	Main findings on functional status change
Pharmacological treatment of AF						
PIAF[2]	• n = 252 • Mean (SD) age, 61 (10) y • Pe-AF • No CHF	Diltiazem (± digoxin, BB)	Amiodaron (± ECV)	6MWT	1	Significant increase in 6MWTD after 12 weeks with rhythm control compared with rate control
AFFIRM[2]	• n = 4060 • Age >65 y • Recurrent AF • High risk for stroke or death; HF (23%)	CCB, BB, or digoxin (<80 bpm at rest and <110 bpm at 6MWT)	Amiodaron (63%), sotalol, dofetilide, IA or IC class (± ECV)	NYHA class, CCS class + 6MWT	3.5	NYHA class worsening with time in both groups and no differences in NYHA/CCS classes between 2 strategies were observed. Presence of AF was associated with worse NYHA class. Rhythm control yielded a modest increase in 6MWTD (94 feets) over rate control (*P* = 0.049).
STAF[2]	• n = 200 • Mean (SD) age, 66 (9) y • Recurrent Pe-AF • NYHA ≥II (56%)	CCB, BB, or digoxin	ECV + IC class/sotalol, or amiodarone (42%) in HF patients	NYHA class	1.6	No significant difference in NYHA functional class was detected between the rate and rhythm control.
HOT CAFE[2]	• n = 205 • Age, 50–75 y • First Pe-AF • HF (70%)	CCB, BB, or digoxin (<90 bpm at rest, <140 with moderate exercise)	ECV + propafenone, disopyramide, sotalol, amiodarone (57%)	NYHA class + Treadmill exercise test	1.7	Both strategies led to similar and significant (*P* <0.001) improvement in NYHA class. Only the rhythm control resulted in significant increase in maximal workload at treadmill test (from 5.2 to 7.6 METs, *P* <0.001). Better increase in exercise duration with rhythm control.
CRAFT[11]	• n = 144 • Mean (SD) age, 38 (10) y • Pe-AF • Rheumatic valvular disease	Diltiazem (n = 48) (<90 bpm at rest and <130 bpm with activity)	Amiodarone (n = 48) or placebo (n = 48) (± ECV)	NYHA class + Treadmill exercise test (Bruce)	1	Treadmill exercise time was longer in patients with sinus rhythm than in those with rate control (mean [SD], 2.6 [1.9] min vs 0.6 [2.5] min; *P*=0.001). Patients with sinus rhythm more commonly improved NYHA class ≥1 than those with rate control (60% vs 17.5%, *P* = 0.014).
Ökçün et al[9]	• n = 154 • Mean age, 58 y in the rate--control and 61 y in the rhythm--control arm • AF >48 h • Nonishemic DCM (LVEF <50%)	Digoxin + metoprolol (<80 bpm at rest)	Cardioversion (IV amiodarone ± ECV) + oral amiodarone	Treadmill exercise test (Bruce)	3	At 1 year, exercise duration and maximal workload significantly improved with rhythm but not with rate control. At 1 year (vs baseline), exercise duration (mean [SD], 9.1 [2.5] min vs 7.3 [1.3] min, *P* <0.001) and maximum workload (mean [SD], 6.3 [1.5] METs vs 5.4 [0.9] METs) were better with rhythm than with rate control.
AF-CHF[2]	• n = 1376 • Mean (SD) age, 67 (11) y • PAF or Pe-AF • LVEF ≤35% • CHF (NYHA ≥2)	BB + digoxin (<80 bpm at rest and <110 bpm at 6MWT)	Amiodarone (82%), sotalol, dofetilide (± ECV)	NYHA class + 6MWT	3.1	No difference in NYHA class improvement between rate and rhythm control. NYHA class improvement was greater with a "high" vs "lower" prevalence of sinus rhythm. The 6MWTD increased to a similar extent with both rate and rhythm control and with both "high" and "lower" prevalence of sinus rhythm.

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Study	Participants	Rate control	Rhythm control	Functional status test	Mean follow-up, y	Main findings on functional status change
Yildiz et al[10]	• n = 221 • Mean age, 57 y in the rate-control and 61 y in the rhythm-control arm • AF >48 h • hypertension	Digoxine, verapamil, and metoprolol (<80 bpm at rest)	Cardioversion (IV amiodarone ± ECV) + oral amiodarone	Treadmill exercise test (Bruce)	3.3	At 1 year exercise duration and maximal worload increased significantly from pre-intervention values only with rhythm (mean [SD], 7.1 [2.7] min vs 9.1 [2.7] min, *P* <0.001 and 5.3 [1.4] METs vs 6.3 [1.4] METs, *P* <0.001) but not with rate control.
CAFE-II[2]	• n = 61 • Mean (SD) age, 72 (7) y • Pe-AF • HF (NYHA ≥2)	Digoxin, BB (<80 bpm at rest and <110 bpm at 6MWT)	Amiodarone (± ECV)	NYHA class + 6MWT	1.2	No differences in NYHA class change over time between 2 strategies. Similar change in 6MWTD was observed with both strategies. The mean increase in 6-MWD was better in patients who remained in sinus rhythm than in those with adequate rate control (210 m vs 21 m, *P* = 0.048).
Catheter-ablation treatment for AF						
PABA-CHF[13]	• n = 81 • Mean age, 61 y in the rate-control and 60 y in the rhythm-control arm • PAF or NPAF • LVEF <40% • NYHA II or III	AV node ablation + biventricular pacing (+ ICD)	PVI	6MWT	0.5	At 6 months the mean 6MWTD increment was greater after PVI than after AV node ablation (71 m vs 16 m, *P* <0.001). 6-month AF progression rate was lower after PVI than after AV node ablation (0% vs 30%, *P* <0.001).
MacDonald et al[13]	• n = 41 • Mean age, 64 y in the rate-control and 62 y in the rhythm-control arm • Pe-AF • NYHA II–IV • LVEF <35%	BB + digoxin, if 24h mean rate was >80 bpm	AF ablation (stepwise approach)	6MWT	0.5	Among patients with advanced HF, there was no difference between AF ablation and medical rate control for change in 6MWTD.
Jones et al[13]	• n = 52 • Mean (SD) age, 63 (9) y • Pe-AF • Symptomatic HF (NYHA II–IV) • LVEF ≤35%	BB, digoxin (<80 bpm at rest and <110 bpm at 6MWT)	LA ablation (PVI + LA lines + CFAE)	6MWT + spiroergometry (treadmill)	1	At 1 year VO_{2max} had increased by 2.13 ml/kg/min in the ablation arm compared with a decrease of 0.94 ml/kg/min in the rate-control arm (*P* = 0.018). Exercise time prolonged (by 133 s) significantly only after ablation. 6MWTD showed tendency toward a nonsignificant increase (by 21 m) after ablation.
Hunter et al[13]	• n = 60 • Mean age, 60 y in the rate-control and 55 y in the rhythm-control arm • Pe-AF + adequate rate control[a] • NYHA II–IV • LVEF <50%	BB	AF ablation (stepwise approach)	NYHA class + Spiro-ergometry (treadmill)	0.5–1	At 6 months after intervention, VO_{2max} was significantly greater in HF patients who underwent AF ablation than in those continuing with medical rate control.

TABLE 1 Randomized studies comparing effects of rate- and rhythm-control strategies on symptomatic and functional status in atrial fibrillation patients (continued from the previous page)

Study	Participants	Rate control	Rhythm control	Functional status test	Mean follow-up, y	Main findings on functional status change
CAMERA-MRI[12]	• n = 68 • Mean age, 62 y in the rate-control and 59 y in the rhythm-control arm • Pe-AF • Idiopathic DCM with LVEF ≤45%	BB (resting rate <80 bpm; an average 24-h rate <100 bpm; post-6MWT rate <110 bpm)	AF ablation (PVI + posterior LA wall isolation)	NYHA class + 6MWT	0.5	At 6 months NYHA class significantly improved in the ablation group compared with the medical rate control group with a mean decrease in NYHA class of 0.82 (*P* <0.001). 6MWTD significantly improved from baseline with both treatments, but with no significant difference between the treatments.
CASTLE-AF[14]	• n = 363 • Median age, 64 y • PAF and Pe-AF • NYHA II–IV • LVEF ≤35% • ICD or CRT-D	70% medical rate control (60–80 bpm at rest and 90–115 bpm at moderate exercise)	AF ablation (PVI ± substrate-based ablation)	6MWT	5	In HF patients at 12 months, the 6MWTD change from baseline was better in those who underwent AF ablation than in those who continued with medical treatment (mean [SD], 52.7 [10.6] m vs 7.1 [13.7] m, *P* = 0.007). This difference was lost at 3 years.

a Adequate rate control was defined as a heart rate lower than 80 bpm at rest and lower than 110 bpm on moderate exertion as assessed on ambulatory monitoring and exercise testing.

Abbreviations: 6MWT, 6-minute walk test; 6MWTD, 6-minute walk test distance; AF, atrial fibrillation; AV, atrioventricular; BB, β-blocker; CCB, calcium channel blocker; CCS, Canadian Cardiovascular Society; CFAE, complex fragmented atrial electrograms; CHF, congestive heart failure; CRT-D, Cardiac Resynchronization Therapy-Defibrillator; DCM, dilated cardiomyopathy; ECV, electrical cardioversion; EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter-defibrillator; IV, intravenous; LA, left atrium; LVEF, left ventricular ejection fraction; MET, metabolic equivalent; NPAF, nonparoxysmal atrial fibrillation; NYHA, New York Heart Association; PABA-CHF, Pulmonary Vein Antrum Isolation vs AV Node Ablation With Biventricular Pacing for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure trial; PAF, paroxysmal atrial fibrillation; Pe-AF, persistent atrial fibrillation; PVI, pulmonary vein isolation; VO_{2max}, maximum oxygen uptake; for full names of the remaining trials, see text.

capacity estimated by different tests in the same patient cohort has been reported.[2,4,9-14]

An objective and reproducible assessment of symptoms and functional status in AF patients is highly relevant for optimization of integrated AF management. Further research is needed to identify reliable tools for such assessment and improve informed patient involvement in shared decision making regarding treatment choices and anticipated outcomes.

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