https://doi.org/10.35336/VA-1335

RHYTHM CONTROL STRATEGY IN ATRIAL FIBRILLATION: STATE OF THE ART

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The use of early rhythm control and catheter ablation is an actively developing direction in the treatment of atrial fibrillation. The review presents studies published from 2021 to 2024, the results of which have the potential to strengthen evidence on the early rhythm control and allow to expand the recommendations for the use of catheter ablation with evidence-based medicine principles.

Key words: atrial fibrillation; rhythm control strategy; catheter ablation; clinical guidelines

Conflict of interest: none.
Funding: none.
Received: 07.02.2024 **Revision received:** 12.03.2024 **Accepted**: 14.03.2024
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For citation: Kanorskii SG, Polishchuk LV. Rhythm control strategy in atrial fibrillation: state of the art. *Journal of Arrhythmology*. 2024;31(2): e5-e14. https://doi.org/10.35336/VA-1335.

The emerging trend in improving therapy for patients with atrial fibrillation (AF) focuses on early rhythm control and identifying indications for catheter ablation as first-line therapy. The topic of early rhythm control in AF has 92 publications in the PubMed database over the past 3 years (2021 to 2024), including 8 randomized clinical trials. The review presents data from 28 papers, all of which meet the methodological quality criteria outlined in the Cochrane Handbook. The results from these studies have the potential to strengthen the evidence supporting the need for early rhythm control. This provision becomes particularly important given the development of the concept of AF as a continuum with progression of arrhythmia to a permanent form. The second part of the review presents 12 studies on the topic of catheter ablation in AF, with results published from 2021 to 2023. These studies allow us to expand the recommendations for using this technique for sinus rhythm control, based on the principles of evidence-based medicine.

STUDIES THAT HAVE STRENGTHENED THE POSITION OF RHYTHM CONTROL STRATEGIES IN PATIENTS WITH ATRIAL FIBRILLATION

In 2022 published a study by E. Marcusohn et al. [1], devoted to the factors associated with the recovery of left ventricular (LV) function in patients with cardiomyopathy due to AF (its diagnosis was based on the exclusion of other causes of heart failure and recovery of LV function after return to sinus rhythm). The aim of the study was to identify clinical and echocardiographic factors associated with the improvement in LV systolic function after electrical cardioversion or catheter ablation in patients with reduced LV ejection fraction (EF) due to atrial fibrillation AF-induced cardiomyopathy. The study included patients with initially preserved LVEF (during sinus rhythm), decreased LVEF as a result of the influence of AF, and improved LVEF after restoration of sinus rhythm. The authors compared the data of those patients in whom LVEF increased to baseline normal levels with those in whom no such effect was observed. In 86 patients with AF, there were signs of decreased LV systolic function and improved EF after return to sinus rhythm, with 64% of patients restoring EF to baseline. Patients with a history of ischemic heart disease, lower LVEF, and larger LV size in AF-induced cardiomyopathy were less likely to return to a level of normal LV function after restoration of sinus rhythm. The study had several limitations: echocardiography was performed by five specialists, introducing the possibility of variability in result interpretation. Additionally, LV function was assessed using transesophageal rather than transthoracic echocardiography. The results may be related to inaccurate ultrasound diagnosis of arrhythmia-associated cardiomyopathy but, on the other hand, may indicate the need for earlier initiation of treatment of AF with reduced EF to improve outcomes.

The American College of Cardiology, American Heart Association, American College of Thoracic Physicians, and Heart Rhythm Society (ACC/AHA/ACCP/HRS) included this study in their 2023 recommendations as support for a grade 1 (upward revision from 2019 recommendations) provision: patients with reduced EF function and persistent AF (or with a high burden of AF) should be advised to attempt rhythm control to assess whether AF contributes to reduced EF function [2]. The European Society of Cardiology (ESC) 2020 Recommendations in this regard include the following provisions: 1) catheter ablation of AF is recommended for the purpose of reverse remodeling of LV dysfunction in patients with AF when there is a high probability of tachyinduced cardiomyopathy regardless of symptoms (class I); 2) catheter ablation should be considered in selected patients with

heart failure and low LVEF to improve survival and reduce the number of hospitalizations related to heart failure (IIa) [3].

A study by J.G.Andrade et al (2021) focused on cryoablation or drug treatment as first-line therapy for AF [4]. The authors randomized 303 patients with symptomatic, previously untreated paroxysmal AF to undergo cryoablation or receive antiarrhythmic drug therapy for rhythm control. All patients had a cardiac monitoring device implanted to detect atrial tachyarrhythmias. The follow-up period was 12 months. The primary endpoint was the first documented recurrence of any atrial tachyarrhythmia (AF, atrial flutter, or atrial tachycardia) between days 91 and 365 after catheter ablation or initiation of antiarrhythmic drug. After 1 year, recurrence of atrial tachyarrhythmias was reported in 66 of 154 patients (42.9%) in the ablation group and 101 of 149 patients (67.8%) in the medical antiarrhythmic therapy group (hazard ratio [HR] 0.48; 95% confidence interval [CI] 0.35-0.66; P<0.001). Symptomatic atrial tachyarrhythmia recurred in 11.0% of patients who underwent ablation and in 26.2% of patients receiving antiarrhythmic drugs (HR 0.39; 95% CI 0.22-0.68). Serious adverse events occurred in 5 patients (3.2%) undergoing ablation and in 6 patients (4.0%) receiving antiarrhythmic drugs.

The J.G.Andrade et al study was included in the ACC/AHA/ACCP/HRS recommendations to support a class 2a provision: in patients with symptomatic AF, rhythm control should be considered for symptom improvement [2]. The ESC document in 2020 assigned a class I recommendation: rhythm control therapy is recommended to improve symptoms and quality of life in patients with symptomatic AF [3].

The work of D.Kim et al (2021) presented a nationwide cohort study of the timing of treatment and effects of rhythm control strategy in patients with AF [5]. The authors aimed to determine whether the results of rhythm control strategies differ depending on the time between the diagnosis of AF and the initiation of treatment. The study included 22,635 adult patients with AF and cardiovascular disease who had recently started treatment according to a rhythm control strategy (antiarrhythmic drugs or ablation) or a ventricular rate control strategy for AF between July 28, 2011, and December 31, 2015. A combined outcome was recorded: death from cardiovascular causes, ischemic stroke, hospitalization for heart failure or myocardial infarction. In the study population, the mean age was 70 years and the duration of follow-up was 2.1 years. Among patients with early treatment of AF (initiated within one year of diagnosis), rhythm control was associated with a lower risk of the primary combined outcome (HR 0.81; 95% CI 0.71-0.93; P=0.002). However, in patients with late treatment of AF (one year or more after diagnosis), no difference in the risk of the primary combined outcome was found between rhythm control and rate control (HR 0.97; 95% CI 0.78-1.20; P=0.76). There were also no significant safety differences between rhythm and frequency control strategies across treatment time. Earlier initiation of treatment was linearly associated with more favorable cardiovascular outcomes for rhythm control compared with frequency control. Consequently, early initiation of rhythm control in D. Kim et al. was associated with a lower risk of adverse cardiovascular outcomes when compared with a rate control strategy in patients with newly diagnosed AF. This association was not detected in patients who had suffered from AF for more than one year.

In 2022, an article by J. Dickow et al. was published on the applicability of the EAST-AFNET 4 study results in routine practice. The EAST-AFNET 4 study demonstrated the clinical benefit of an early rhythm control strategy in patients with first-onset atrial fibrillation (AF) and concomitant cardiovascular diseases. The authors identified 109739 patients with newly diagnosed AF similar to the design of the EAST-AFNET 4 trial during the recruitment period. Patients were classified as receiving early rhythm control with ablation or antiarrhythmic drug therapy within the first year after diagnosis of AF (n=27106) or not receiving early rhythm control (control group; n=82633). After applying the propensity score matching statistical technique, Cox regression was used to compare the groups by the primary combined outcome, which included death from any cause, stroke, hospitalization for heart failure, or myocardial infarction. The majority of patients (79948 of 109739; 72.9%) met the inclusion criteria for EAST-AFNET 4. Early rhythm control was associated with a reduced risk of primary combined outcome (HR 0.85; 95% CI 0.75-0.97; P=0.02) with significant concordance of outcomes between patients who met (HR 0.89; 95% CI 0.76-1.04; P=0.14) and did not meet EAST-AFNET 4 inclusion criteria (HR 0.77; 95% CI 0.60-0.98; P=0.04). Early rhythm control was associated with a lower risk of stroke in both the overall cohort and in patients who met inclusion criteria in EAST-AFNET 4. This analysis confirmed the clinical benefit of early rhythm control observed in EAST-AFNET 4 and the need to consider it as an effective treatment option for newly diagnosed AF.

The work of D.Kim et al. and J.Dickow et al. and the EAST-AFNET 4 study were the basis for a new ACC/AHA/ACCP/HRS recommendation in 2023: rhythm control should be considered for patients with newly diagnosed AF (<1 year) to reduce the risk of hospitalization, stroke, and death (2a) [2]. The EAST-AFNET 4 data were not included in the 2020 ESC recommendations for AF due to near-simultaneous submission, and the provisions of the ESC document relate primarily to symptomatic patients. In particular, catheter-based pulmonary vein isolation should be considered as first-line therapy for rhythm control to improve symptoms in selected groups of patients with symptomatic episodes of paroxysmal AF (IIa recommendation). It can also be considered in patients with symptomatic persistent AF without major risk factors for recurrent AF as an alternative to class I and III antiarrhythmic drugs, taking into account patient choice, benefits, and risks (IIb recommendation) [3].

A.Rillig et al. conducted the EAST-AFNET 4 subanalysis on early rhythm control in patients with AF and heart failure [8]. The paper evaluated the effect of early rhythm control therapy versus conventional treatment (rhythm control only for symptom improvement) on two primary outcomes of the trial and on selected secondary outcomes in patients with New York Heart Association class II-III heart failure symptoms or LVEF <50%. A to-

tal of 798 patients (37.6% women, mean age 71.0 years, 785 with known LVEF) were included in the analysis. The majority of patients (n=442) were diagnosed with heart failure with preserved LVEF (LVEF≥50%; mean LVEF 61±6.3%), 211 patients had heart failure with moderately reduced LVEF (LVEF 40-49%; mean LVEF 44±2.9%), and 132 patients had heart failure with reduced LVEF (LVEF<40%; mean LVEF 31±5.5%). The median follow-up was 5.1 years. The combined primary outcome of cardiovascular death, stroke, or hospitalization for worsening heart failure or acute coronary syndrome occurred less frequently in patients randomized to early rhythm control (94/396; 5.7 per 100 patient-years) compared with patients randomized to «usual care» (130/402; 7.9 per 100 patient-years; HR 0.74; 95% CI 0.56-0.97; P=0.03), regardless of heart failure status (P=0.63). At the same time, LVEF improved in both groups (absolute change in LVEF after 2 years was 5.3±11.6% in the early rhythm control group and 4.9±11.6% in the «usual care» group; P=0.43). This work confirmed that rhythm control therapy has clinical benefit when initiated within 1 year after diagnosis of AF in patients with signs or symptoms of heart failure.

Also, the issue of features of AF therapy in heart failure was analyzed by D.L.Packer et al. based on the results of comparison of ablation and drug therapy of AF in heart failure in participants of the CABANA study [9]. In this project, 2204 patients with AF aged ≥65 years or <65 years and with ≥1 risk factors for stroke were randomized into groups of catheter ablation for pulmonary vein orifice isolation or drug therapy that included drugs that controlled ventricular rate or sinus rhythm. A total of 778 (35%) of the study participants had baseline heart failure >II functional class according to the New York Heart Association classification. The primary endpoint of the CABANA trial was combined (death, disabling stroke, major bleeding, or resuscitation for sudden cardiac arrest). In this CABANA fragment, 378 patients received ablation and 400 received drug therapy for AF. LVEF at baseline was available in 571 patients (73.0%) and was <40% in 9.3% of them and 40-50% in 11.7%. The ablation group had a 36% reduction in the incidence of the primary combined endpoint (HR 0.64; 95% CI; 0.41-0.99) and a 43% reduction in the risk of all-cause mortality (HR 0.57; 95% CI 0.33-0.96) compared with drug therapy, with a median follow-up period of 48.5 months. The incidence of recurrent AF was lower in the ablation group (HR 0.56; 95% CI 0.42-0.74). The adjusted mean difference for the total AFEQT questionnaire score, averaged over the entire 60-month follow-up period, was 5.0 points (95% CI 2.5 to 7.4 points) and for the frequency of symptoms from the MAFSI list was 2.0 points in favor of the ablation group (95% CI; -2.9 to -1.2). In summary, in CABANA participants with chronic heart failure diagnosed at the time of study inclusion, catheter ablation resulted in reduced recurrence of AF, improved survival, and improved quality of life compared with drug therapy. At the same time, the majority of patients had preserved LV function.

The data of A.Rillig et al. and D.L.Packer et al. confirmed the provision of ACC/AHA/ACCP/HRS 2023 recommendations: for patients with AF and heart failure, rhythm control should be considered to improve symptoms and outcomes (such as death and hospitalization for heart failure or ischemia) (2a) [2].

Within the framework of the view of AF as a progressive staging disease, the issue of slowing the progression of AF is an important one. In this context, the works of T. Koldenhof et al. are referenced (showing that in patients with first-diagnosed paroxysmal atrial fibrillation, the use of verapamil was associated with less progression of atrial fibrillation compared to the use of beta-adrenoblockers or no frequency control) as well as W.Y. Yang et al. Recent work has identified clinical factors associated with progression of AF by analysis of the China Registry. Of the 8290 patients with paroxysmal AF included in the study, 50% underwent primary AF ablation. The primary outcomes were ischemic stroke/systemic embolism, hospitalization for cardiovascular causes, death from cardiovascular causes, and death from any cause. The median follow-up duration was 1091 days, progression of AF to persistent form occurred in 881 (22.5%) patients in the no-ablation group, whereas only 130 (3.0%) patients in the ablation group relapsed and developed persistent AF. Older age, longer history of AF, heart failure, arterial hypertension, coronary heart disease, respiratory disease, and larger atrial diameter were associated with progression of AF, whereas use of antiarrhythmic drugs and AF ablation were associated with no progression of arrhythmia. In patients in the non-ablation group, progression of AF was independently associated with an increased risk of ischemic stroke/embolism (HR 1.52; 95% CI 1.15-2.01) and hospitalization for cardiovascular causes (HR 1.40; 95% CI 1.23-1.58).

The available data on the progression of AF led the ACC/AHA/ACCP/HRS experts to make a recommendation in 2023: for patients with AF, a rhythm control strategy should be considered to reduce the likelihood of AF progression (2a) [2]. The ESC guidelines in 2020 noted that «the true impact of different therapeutic interventions at different stages of the disease on the progression of AF is not clearly defined» [3].

The next direction of modern research is the study of the role of symptoms in the choice of treatment tactics for AF. D.Sgreccia et al. in 2021 published a systematic review and meta-analysis comparing outcomes in asymptomatic and symptomatic AF (death from any cause, cardiovascular death and thromboembolic events), including data from 81462 patients [12]. Twenty-six percent of patients had AF characterized as asymptomatic, and 74% had symptoms. No differences were found between these patient groups with respect to the risks of all-cause mortality (HR 1.03; 95% CI 0.81-1.32), death from cardiovascular causes (HR 0.87; 95% CI 0.54-1.39), risk of stroke (HR 1.22; 95% CI 0.77-1.93), and stroke or systemic thromboembolism (HR 1.06; 95% CI 0.86-1.31).

S.Willems et al. analyzed the early rhythm control strategy for symptomatic and asymptomatic (modified EHRA class I) AF in the EAST-AFNET 4 study. The clinical benefit of early systematic rhythm control did not differ between asymptomatic and symptomatic patients [13].

A.N.L.Hermans et al. [14] showed that in patients with persistent AF, assessment of self-reported symp-

toms related to rhythm control with electrical cardioversion once before cardioversion and once during the 1-month follow-up after cardioversion rarely revealed a correlation between symptoms and rhythm pattern. Better methods are needed to assess the relationship between symptoms and heart rate in patients with persistent AF.

Published work in this area has led experts from the American College of Cardiology (ACC), American Heart Association (AHA), American College of Chest Physicians (ACCP), and Heart Rhythm Society (HRS) to conclude that in patients with atrial fibrillation (AF), when the contribution of AF to symptomatology is unclear, an attempt at rhythm control (e.g., cardioversion or pharmacologic therapy) may be considered to determine the relationship of symptoms to AF (2b recommendation) [2].

N.Bodagh et al. performed a systematic review of the effect of catheter ablation on cognitive function in AF compared to drug therapy [15]. There were no significant differences in the effects of the two arrhythmia treatments on cognitive decline. D.Kim et al. [16] presented a nationwide population-based cohort study of the relationship between rhythm control and dementia in patients with AF. We included 41135 patients with AF receiving anticoagulant therapy who were first treated for sinus rhythm control (antiarrhythmic drugs or ablation) or ventricular rate control between January 1, 2005 and December 31, 2015. The primary outcome was dementia, and the statistical technique of propensity score matching was used. In the study population (46.7% women; mean age 68 years), 4039 patients were diagnosed with dementia during a mean follow-up period of 51.7 months. Rhythm control versus frequency control was associated with a reduced risk of dementia (weighted incidence rate 21.2 vs 25.2 per 1000 person-years; adjusted HR 0.86; 95% CI 0.80-0.93). The association between rhythm control and reduced risk of dementia was observed even after adjustment for stroke development (adjusted HR 0.89; 95% CI 0.82-0.97) and was more prominent in relatively younger individuals and patients with lower CHA_2DS_2-VASc scores. Among dementia subtypes, rhythm control was associated with a lower risk of Alzheimer's disease (adjusted HR 0.86; 95% CI 0.79-0.95).

The issues of cardiac remodeling were devoted to the works of Y.Abe et al. [17] and L.Soulat-Dufour et al. [18]. The second study reported that restoration of sinus rhythm reversed cardiac remodeling and reduced valve regurgitation in patients with first diagnosed AF, as demonstrated by serial three-dimensional transthoracic echocardiography in 117 patients hospitalized for atrial fibrillation at admission, 6 months, and 12 months. In 47 patients with active restoration of sinus rhythm by cardioversion and/or ablation, there was a decrease in all indexed atrial volumes, right ventricular end-systolic volume, an increase in LV end-diastolic volume, and improved function of all four chambers of the heart.

These works support the ACC/AHA/ACCP/HRS experts' recommendation: in patients with AF, a rhythm control strategy can be considered to reduce the likelihood of dementia or worsening structural heart disease (2b) [2].

STUDIES STRENGTHENING THE POSITION OF CATHETER ABLATION IN PATIENTS WITH ATRIAL FIBRILLATION

An important result of studies in recent years that have led to changes in clinical guidelines for the treatment of AF is the superiority of catheter ablation over pharmacologic therapy for rhythm control in certain categories of patients. In the AHA/ACC/ACCP/HRS guidelines, the class of this recommendation has been updated from 2a to 1. The basis for this change was data from the EARLY-AF and STOP AF First studies.

The work of O.M.Wazni et al. STOP AF First evaluated cryoballoon ablation as initial therapy for AF involving patients aged 18 to 80 years with paroxysmal AF [19]. Participants who had not previously received rhythm control therapy were randomized 1:1 to treatment with class I or III antiarrhythmic drugs or pulmonary vein orifice isolation with cryoballoon ablation. Arrhythmia monitoring included: 12-lead electrocardiography performed at baseline, 1, 3, 6, and 12 months; patient-activated transtelephonic monitoring performed weekly and when symptoms were present at 3 to 12 months; and 24-hour ambulatory monitoring at 6 and 12 months. The primary efficacy end point was treatment success, defined as the absence of primary procedure failure or recurrence of atrial tachyarrhythmias after a 90-day blinded period, assessed by Kaplan-Meier analysis. The primary safety endpoint was evaluated in the ablation group only and represented the composite of serious adverse events associated with the procedure. Of 203 participants, 104 underwent ablation and 99 received drug therapy. In the ablation group, initial procedural success was achieved in 97% of patients. In Kaplan-Meier analysis, the proportion of patients with successful treatment at 12 months was 74.6% (95% CI 65.0-82.0) in the ablation group and 45.0% (95% CI 34.6-54.7) in the drug therapy group ($P<0.001$). There were two safety related events in the ablation group. Consequently, cryoballoon ablation as initial therapy was superior to drug treatment in the prevention of atrial arrhythmia recurrence in patients with paroxysmal AF.

J.G.Andrade et al. in the EARLY-AF study [20] compared the progression of AF after cryoablation or drug therapy. The hypothesis of the work was the notion that catheter ablation as initial therapy can influence the pathogenetic mechanism of AF and stop the progression to a persistent form of arrhythmia. The authors reported a three-year follow-up of patients with paroxysmal AF who were untreated before inclusion in the study and randomized to initial rhythm control therapy with cryoballoon ablation or to treatment with antiarrhythmic drugs. All patients were fitted with implantable loop recorders and assessed by downloadable daily recordings and in-person visits every 6 months. Data were recorded on first episode of AF lasting ≥7 days or 48 hours to 7 days but requiring cardioversion for termination, recurrence of atrial tachyarrhythmias defined as AF, atrial flutter, or tachycardia lasting ≥30 s, burden of AF, and measures of quality of life, care-seeking, and safety data were recorded. A total of 303 patients were included in the study, of whom 154 patients received primary rhythm control therapy with cryoballoon ablation and 149 patients

received antiarrhythmic drug therapy. During 36 months of follow-up, 3 patients (1.9%) in the ablation group developed an episode of persistent AF compared with 11 patients (7.4%) in the medical treatment group (HR 0.25; 95% CI 0.09-0.70). Atrial tachyarrhythmias occurred in 87 patients in the ablation group (56.5%) and 115 in the antiarrhythmic drug group (77.2%) (HR 0.51; 95% CI 0.38-0.67). At 3 years, 8 patients (5.2%) in the ablation group and 25 (16.8%) in the antiarrhythmic drug group were hospitalized (HR 0.31; 95% CI 0.14-0.66), and serious adverse events occurred in 7 (4.5%) and 15 (10.1%) patients, respectively. Thus, initial treatment of paroxysmal AF with catheter-based cryoballoon ablation was associated with a lower incidence of persistent AF or recurrent atrial tachyarrhythmias during 3 years of follow-up compared with initial use of antiarrhythmic drugs.

The work of K.Yalin et al. was devoted to catheter ablation for AF in patients under 30 years of age [21]. Fifty-one patients (mean age 24.0±4.2 years, 78.4% male) with drug-resistant paroxysmal AF participated in the study. The subjects did not have structural heart disease or a family history of AF. Electrophysiologic study revealed supraventricular tachycardia in 12 patients (23.5%): orthodromic atrioventricular re-entry tachycardia with a hidden additional conduction pathway (3 patients); typical atrioventricular nodal re-entry tachycardia (6 patients); tachycardia with a focus in the region of the left superior pulmonary vein, tachycardia with a focus in the region of the left atrial appendage, and typical atrial flutter (1 patient each). In patients with electrophysiologically induced supraventricular tachycardias, ablation without pulmonary vein isolation was performed as an index procedure, except for the patient with atrial flutter, who underwent ablation of the cavotricuspid isthmus in addition to pulmonary vein isolation. The remaining patients underwent radiofrequency (29.4%) or cryoballoon (47%) pulmonary vein isolation. No serious complications related to the ablation procedure were reported. Follow-up was based on outpatient visits, including 24-hour Holter electrocardiogram monitoring at 3, 6, and 12 months after ablation. In case of symptoms suggestive of arrhythmia recurrence, additional daily monitoring was ordered. Recurrence was defined as an episode of any atrial tachyarrhythmia >30 s after a 3-month blinded period. A total of 2 patients with atrioventricular nodal re-entry tachycardia and 1 patient with left atrial tachycardia from appendage had a recurrence of AF within the first 3 months and underwent pulmonary vein isolation. After a 3-month blinded follow-up period of 17.0±10.1 months, no recurrence of atrial tachyarrhythmias was recorded in 44 of 51 patients (86.2%). In the pulmonary vein isolation group, 33 of 39 patients (84.6%) had no recurrence of atrial tachyarrhythmias. The authors concluded that the substrate of supraventricular tachycardia is identified in approximately one quarter of young patients with a history of AF, and targeted ablation without pulmonary vein isolation may be sufficient in these patients. At the same time, pulmonary vein isolation is necessary in most patients and is safe and effective in this population.

I. El Assaad et al. [22] studied the management and outcomes of AF in young children and adults in a multicenter study including patients under 21 years of age with documented AF from January 2004 to December 2018. Demographic data, family and clinical history, electrophysiological parameters, and results of AF treatment were analyzed, among others. Patients with comorbidities were excluded from the study. Of 241 patients (83% male; mean age of onset, 16 years), recurrence of AF was observed in 94 (39%) during 2.1±2.6 years of follow-up. In multivariate analysis, family history of this arrhythmia in first-degree relatives <50 years of age (HR 1.9; P=0.047) and longer PR interval duration during sinus rhythm (HR 1.1 per 10 ms; P=0.037) were predictors of recurrent AF. AF recurrence was independent of «no treatment» (39/125, 31%), initiation of daily antiarrhythmic drug therapy (24/63, 38%), or performance of ablation (14/53, 26%; P=0.39). Only ablation of non-AF substrate for supraventricular tachycardia contributed to the absence of AF recurrence (P=0.013).

D.S.Chew [23] evaluated the cost-effectiveness of catheter ablation compared with the use of antiarrhythmic drugs in the treatment of AF in the United States according to the CABANA study. In this project, catheter ablation did not significantly reduce the incidence of the primary endpoint (death, disabling stroke, major bleeding, or resuscitation for cardiac arrest) compared with drug therapy, but did improve quality of life and reduce the risk of recurrent AF. In the subgroup of patients with heart failure, ablation improved not only quality of life but also survival. Cost-effectiveness was a secondary endpoint in the CABANA study, included the calculation of an incremental cost-effectiveness ratio (ICER - the ratio of the difference in cost to the difference in effectiveness between an intervention and a comparison technology reflects the incremental value of an additional unit of effectiveness of a medical technology [24]). Given that the ICER reference value in the US is implicit, it was concluded that in the CABANA study catheter ablation was economically attractive compared with drug therapy in general when assessing ICER per predicted Quality-Adjusted Life Years (QALY), but not per life year in general.

K-H.Kuck et al. [25] compared the effect of catheter ablation and drug therapy on slowing the progression of AF in the ATTEST study, showed that radiofrequency catheter ablation is superior to drug therapy in slowing the progression of paroxysmal to persistent form of AF. The incidence of persistent AF/atrial tachycardia at 3 years (Kaplan-Meier estimate) was significantly lower in the ablation group (2.4%; 95% CI 0.6-9.4%) than in the antiarrhythmic drug therapy group (17.5%; 95% CI 10.7-27.9%; one-sided P=0.0009).

K.H.Monahan et al. [26] compared the outcomes of ablation and drug therapy depending on the form of AF in the CABANA study. At inclusion, 946 (42.9%) patients were diagnosed with paroxysmal form of AF, 1042 (47.3%) - persistent, 215 (9.8%) - long-term persistent. The following adjusted hazard ratio values for the primary endpoint CABANA (catheter ablation to drug therapy) were obtained: 0.81 (95% CI 0.50-1.30) for patients with paroxysmal, 0.83 (95% CI 0.56-1.22) for patients with persistent, and 0.93 (95% CI 0.36-2.44) for patients with long-standing persistent AF. Ablation was more effective than drug therapy in reducing the risk of first arrhythmia

recurrence in all forms of AF with an adjusted hazard ratio of 0.49 (95% CI 0.39-0.62) for patients with paroxysmal, 0.53 (95% CI 0.43-0.65) for persistent, and 0.64 (95% CI 0.41-1.00) for long-standing persistent AF. Ablation was associated with greater symptom reduction, with the mean difference on the MAFSI scale being in favor of ablation at 5-year follow-up in all subgroups: for paroxysmal AF, the difference was -1.9 points (95% CI -1.2 to -2.6), for persistent AF -0.9 (95% CI -0.2 to -1.6), and for long-standing persistent -1.6 points (95% CI -0.1 to -3.1). Ablation was also associated with greater improvement in quality of life at 5-year follow-up in all subgroups. The overall AFEQT score improved by 5.3 points (95% CI 3.3 to 7.3) in patients with paroxysmal AF compared with the drug therapy group, with a difference of 1.7 points (95% CI 0.0 to 3.7) in persistent AF and 3.1 points (95% CI -1.6 to 7.8) in long-term persistent AF. Although the prognostic effects of catheter ablation treatment compared with drug therapy on the primary endpoint did not differ for all forms of atrial fibrillation (AF), ablation was more effective than drug therapy in reducing the rate of recurrent AF and improving quality of life in all three subgroups.

The role of the form of AF was also studied in the work of D.J. Friedman et al., which focused on changes in the frequency of care and costs within the healthcare system when catheter ablation is used for both paroxysmal and persistent AF. Data from 2794 patients with paroxysmal and 1909 with persistent form of AF who underwent ablation in 2016-2018 were considered. Outcomes assessed included hospitalization, emergency care, physician visits, cardioversion, and use of antiarrhythmic drugs. Cost of care and outcomes were compared one year before and after ablation. Costs in the 12 months after ablation were lower for hospitalizations due to AF (paroxysmal AF -28%, persistent AF -33%), emergency care (paroxysmal AF -76%, persistent AF -70%), on prescription of antiarrhythmic drugs (paroxysmal AF -25%, persistent AF -7%) and cardioversion (paroxysmal AF -59%, persistent AF -55%) compared with 12 months before ablation. Reduced costs were observed in patients with both paroxysmal and persistent AF, but absolute costs remained higher for patients with persistent AF. Total costs of AF treatment were higher at 1 year after ablation compared with the year before ablation (for paroxysmal AF by 11%, P<0.0001; for persistent AF by 10%, P<0.0001) because of repeated ablation. However, at follow-up analysis 18 months later, postablation costs were generally lower (paroxysmal AF -35%, P<0.0001; persistent AF -34%, P<0.0001) despite accounting for the costs of repeat ablation (the extended period was compared with the 6-month period before ablation). The authors concluded that significant reductions in care-seeking and treatment costs were observed among patients with both paroxysmal and persistent AF, and a strategy of earlier ablation may reduce long-term costs in the management of patients with AF.

T.D.Bahnson et al. [28] analyzed the relationship between age and outcomes when comparing catheter ablation and drug therapy of AF according to the CABANA study. Of 2204 randomized patients, 766 (34.8%) were <65 years of age, 1130 (51.3%) were 65-74 years of age, and 308 (14.0%) were ≥75 years of age. Catheter ablation was associated with a reduced incidence of the primary endpoint with an adjusted HR of 0.57 (95% CI 0.30-1.09) for patients aged <65 years, 0.79 (95% CI 0.54-1.16) between 65 and 74 years, and an «indeterminate effect» of 1.39 (95% CI 0.75-2.58) for age ≥75 years. For every 10-year increase in age, the adjusted HR of the primary endpoint of CABANA increased by an average of 27% (P=0.215). A similar trend was observed for all-cause mortality: for every 10-year increase in age, the adjusted HR increased by an average of 46% (P=0.111). The incidence of recurrent AF was lower in the ablation group than drug therapy in all three age subgroups, with adjusted HRs of 0.47, 0.58, and 0.49, respectively. The incidence of treatment-related complications in both groups did not exceed 3% regardless of age. Consequently, the greatest relative and absolute benefits of catheter ablation are seen in younger patients with AF.

The ACC/AHA/ACCP/HRS recommendations in 2023 included a provision that in selected patients (typically young adults with few comorbidities) with symptomatic paroxysmal AF in whom rhythm control is required, catheter ablation should be considered as first-line therapy to improve symptoms and reduce progression to persistent AF (Class 1 recommendation) [2].

Y.Waranugraha et al. [29] investigated the feasibility of prophylactic ablation of the cavotricuspid isthmus in PD without documented typical atrial flutter by conducting a systematic review and meta-analysis. The authors concluded that this intervention was ineffective. After a successful catheter ablation procedure, the risk of atrial tachyarrhythmias (HR 0.08; 95% CI 0.00-0.17; P=0.04) and the rate of recurrent AF (HR 0.07; 95% CI 0.01-0.13; P=0.02) were higher in the pulmonary vein isolation and cavotricuspid isthmus ablation groups compared with the pulmonary vein isolation alone group.

D.Gupta et al. [30] showed that the use of cryoballoon pulmonary vein isolation as first-line therapy for typical atrial flutter is equal in efficacy to standard ablation of the cavotricuspid isthmus to prevent recurrence of atrial tachyarrhythmia and better prevents first-onset AF.

J.Y.Kim et al. [31] presented clinical results of individual treatment strategies for asymptomatic AF using the quality of life scale from the CODE-AF registry (comparative study of drugs for symptom control and prevention of complications of AF). Patients were divided into two groups according to baseline AFEQT score; with a value ≤80, AF was defined as symptomatic, >80 asymptomatic. The primary endpoint was a composite of events: hospitalization for heart failure, ischemic stroke, or death from a cardiovascular cause. The study comprised 1515 patients (mean age, 65.7±10.5 years; 65.9% male), initially divided into two treatment strategy groups for analysis: a rhythm control group (receiving antiarrhythmic drugs, electrical cardioversion, and/or catheter ablation) and a ventricular rate control group (no treatment for rhythm control, including antiarrhythmic drugs). Second, patients were divided into 2 treatment strategy groups according to catheter ablation: catheter ablation group and drug therapy group. If a patient received multiple treatment strategies including catheter ablation, the patient was assigned to the catheter ablation group. The

drug therapy group included patients receiving antiarrhythmic drugs, electrical cardioversion, and/or rhythm control medications. Subgroup analysis was performed on the basis of age, sex, form of AF, LVEF, left atrial diameter, and CHA_2DS_2-VASc. Rhythm control provided a significant reduction in the risk of combined outcome in asymptomatic patients compared with frequency control (HR 0.47; 95% CI 0.27-0.84, P=0.01), but symptom-specific survival was not significantly different between the catheter ablation and drug therapy groups. The best rhythm control results in the asymptomatic group were associated with paroxysmal AF, CHA_2DS_2-VASc ≥3, and left atrial diameter <50 mm.

Therefore, numerous qualitative studies examining the clinical and economic efficacy of catheter ablation have contributed to the described increase in the class of recommendations for the use of this method in the therapy of atrial fibrillation (AF). However, there's an emphasis on clarifying the factors that contribute to the success and safety of the procedure.

CONCLUSION

In recent years, evidence has emerged highlighting the benefits of a strategy to restore and maintain sinus rhythm in patients with AF. This approach has the potential to reduce symptoms, improve quality of life, and lower the risk of heart failure, stroke, and cardiovascular death. The authors of the new US guidelines for AF provide a simple scheme that allows practicing physicians to choose between rhythm control and rate control strategies in specific patients (Fig. 1).

It is obvious that rhythm control is more successfully realized in patients with less severity of the underlying cardiovascular pathology and fewer comorbidities, with paroxysmal form of AF. Better outcomes with catheter ablation should be expected in these patients and should be offered to them. However, in cases where this procedure is not feasible or not available, these patients may also benefit significantly from appropriately selected drug therapy, although the burden of AF with antiarrhythmic drugs may be relatively high. Catheter ablation and drug antiarrhythmic therapy should not be opposed to each other, but should be used when necessary as complementary means of achieving effective rhythm control in patients with AF.

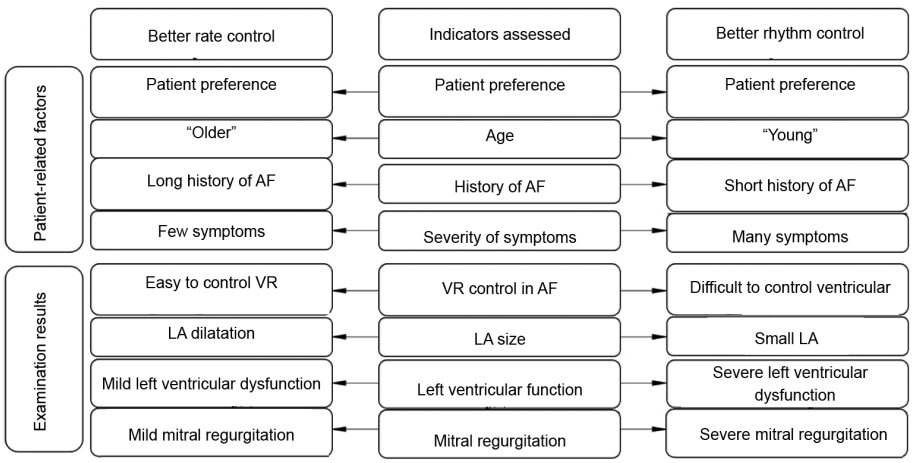

Fig. 1. The choice between rhythm control and rate control in patients with AF. Note: LA, left atrium; AF, atrial fibrillation; VR, ventricular rate.

Positive dynamics of patients' condition will be more noticeable in case of initially greater severity of symptoms, in case of heart failure. Early (diagnosed less than 1 year ago) initiation of therapy to control sinus rhythm can reduce the risk of adverse cardiovascular outcomes in patients with cardiovascular disease. It is likely that also in asymptomatic patients with AF, early restoration of sinus rhythm may be prognostically advantageous and therefore appropriate.

With the accumulation of experience, research data, and advancements in the technique of catheter ablation for AF, evaluations of its efficacy are increasingly positive. It is now recommended as the first-choice therapy in selected patients. Indeed, elimination of trigger pulsation from pulmonary veins is an effective means of preventing AF as long as the atria are not subjected to marked remodeling. In severe atrial cardiomyopathy, in patients with persistent and long-standing forms of AF, the effectiveness of pulmonary vein isolation is significantly lower, and additional effects on the left atrial wall do not bring significant benefit.

It should be noted that much of the evidence base on the relationship between sinus rhythm control and ventricular rate control strategies is based on studies in patients with non-valvular AF, whereas patients with valve heart disease were underrepresented in the main projects. Information on nonpharmacologic treatment of AF in valve heart disease is limited. Current guidelines for the management of patients with non-valvular AF do not apply to patients with this arrhythmia with rheumatic valve disease, who are often younger, female, and have fewer comorbidities.

Ventricular rate control in AF can also be considered as first-choice treatment. It is appropriate to consider catheter ablation when the restoration of sinus rhythm is not expected to be of significant benefit, such as in elderly inactive patients with comorbidities and minimal symptoms of AF. It is also suitable in cases with a low probability or established impossibility of long-term maintenance of sinus rhythm, such as in patients with significant atrial enlargement and fibrosis, or those with persistent/long-standing forms of AF.

Decisions about which strategy to pursue and how to achieve the intended goals should be made in conjunction with the patient, considering the patient's comorbidities, structural heart disease, symptomatology, hemodynamic status, and personal preferences. For example, because AF ablation is an invasive procedure, some patients may prefer to forgo it and opt for antiarrhythmic drug therapy. Efforts to correct known risk factors for recurrent AF (obesity, hypodynamia, unhealthy diet, alcohol, smoking, arterial hypertension, diabetes mellitus, obstructive sleep apnea) depend mainly on patients.

The modern principle of integrated management of patients with AF requires an individualized approach that takes into account patients' unique clinical profiles, preferences, and the potential risks and benefits of treatment strategies.

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