https://doi.org/10.35336/VA-2023-1-07

CHOICE OF SINUS RHYTHM CONTROL STRATEGY IN PATIENTS WITH ATRIAL FIBRILLATION: WHY, WHEN AND HOW? A REVIEW

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After 20 years of dubious notions of parity between sinus rhythm control and ventricular rate control strategies in patients with atrial fibrillation, there is evidence of the prognostic superiority of the former. The review article presents the results of randomized trials that support early rhythm control in patients with atrial fibrillation, possible pharmacological and non-pharmacological methods of such treatment in real clinical practice.

Key words: atrial fibrillation; treatment; antiarrhythmic drugs; catheter ablation; sinus rhythm control

Conflict of Interests: nothing to declare.
Funding: none.
Received: 02.09.2022 **Revision received:** 29.09.2022 **Accepted:** 17.10.2022
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For citation: Kanorskii SG. Choice of sinus rhythm control strategy in patients with atrial fibrillation: why, when and how? A review. *Journal of Arrhythmology.* 2023;30(1): 52-60. https://doi.org/10.35336/VA-2023-1-07.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, which has already been diagnosed in tens of millions of people worldwide. With the increase in life expectancy of the population, the incidence of AF is rapidly increasing and, according to forecasts, by 2050 the number of people with this arrhythmia may increase 3 times. AF increases the risk of morbidity and mortality due to stroke, heart failure, and cognitive dysfunction, even in patients receiving current optimal therapy. Therefore, further optimization of the treatment of AF is required to reduce the incidence of complications of this arrhythmia [1, 2].

There are four main principles in the treatment of AF: reduction of the influence of risk factors and the risk of stroke, ventricular rate control (VRC), and control of sinus rhythm. In accordance with current recommendations, ventricular rate control to maintain hemodynamic stability while maintaining arrhythmia remains the standard therapy for AF, which solves the problem of reducing the severity of symptoms and the incidence of disease outcomes (progression of heart failure, repeated hospitalizations, deaths from cardiovascular and other causes). Rhythm control, which includes cardioversion (pharmacological or electrical), antiarrhythmic drugs (AADs), and/or ablation, is an AF therapy introduced to resolve persistent symptoms of arrhythmia without strong evidence of additional improvement in outcomes compared with VRC. When a rhythm control strategy is chosen, catheter ablation (CA) of AF is considered as a second-line therapy for patients who have failed or are intolerant of at least one AAD [3]. However, it is obvious that such a simplified approach does not include the analysis of a number of situations that are difficult for medical decision-making, often resolved with the obligatory consideration of the opinion of the patient, who insists on medical or interventional treatment. Regardless of which AF management strategy is used, risk factor assessment and therapy are required to prevent thromboembolism. Despite the application of modern clinical guidelines for the treatment of AF, patients remain at risk of developing cardiovascular complications, such as stroke, heart failure, and acute coronary syndrome, associated with cardiovascular mortality of about 5% per year [2].

At the beginning of the 21st century, the position that seemed logical for practitioners about the preference in patients with AF for the strategy of restoring and maintaining sinus rhythm compared to VRC could not be confirmed in several randomized trials [4]. Therefore, over the past 20 years, recommendations for the management of patients with AF have been based on the results of the largest of these studies, AFFIRM (n=4060), which did not show significant differences between VRC and rhythm control strategies when comparing overall mortality and cardiovascular complications. [5]. In the second most important study of that time, RACE (n=522), rate control was compared with a sinus rhythm control strategy in patients with persistent AF who underwent cardioversion [6]. A similar frequency of primary endpoint events (cardiovascular death, heart failure, bleeding, thromboembolic complications, and adverse reactions to AADs) was shown in the VRC and rhythm control groups. Therefore, in the context of a rapid increase in the number of hospitalizations with AF, rate control was recognized as the standard of care for oligosymptomatic/asymptomatic course of this arrhythmia without compromising outcomes, with a favorable tolerability profile of the drugs used for it and cost-effectiveness. Until recently, it was recognized that sinus rhythm control with AADs, electrical cardioversion, and AF ablation reduces symptoms and improves quality of life in patients with symptoms of arrhythmia, but there was insufficient evidence to claim an improvement in cardiovascular outcomes [3, 7].

Meanwhile, several limitations of the mentioned studies should be noted. In AFFIRM and RACE, the average age of participants was over 65 years, that having raised questions about the applicability of their findings to younger patients with AF. In addition, a retrospective analysis of the AFFIRM study showed that the presence of sinus rhythm was associated with a 47% reduction in the risk of death ($p < 0.0001$), although the use of AADs, most commonly amiodarone, to maintain sinus rhythm was associated with an increased risk of adverse events [8]. Finally, discontinuation of anticoagulant therapy in the presence of an impression of maintaining sinus rhythm on rare visits to research centers contributed to an increase in the incidence of ischemic stroke in the rhythm control group (7.1%) compared with the rate control group (5.5%) [5].

In accordance with the principles of the PRISMA systematic review [9], the literature on sinus rhythm control strategy in AF was searched using the PubMed/MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews databases. The keywords “atrial fibrillation” and “rhythm control”, the filters “clinical trial”, “meta-analysis”, “randomized controlled trial”, “review”, “systematic review” were used. After screening 2367 found sources, those of them were selected that reflected modern ideas about the role of sinus rhythm control in the treatment of patients with AF. Preference was given to the most cited articles in journals with a high impact factor and open access to the full text. In this paper, 55 major sources of literature have been cited.

EARLY RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION AND ADVERSE CARDIOVASCULAR OUTCOMES

EAST-AFNET 4 study

It is known that AF itself causes unfavorable electrical and structural remodeling of the atria, developing for several weeks and contributing to the progressive course of arrhythmia [10]. It has been suggested that early intervention to prevent atrial remodeling due to AF could reduce the risk of adverse cardiovascular events. The EAST-AFNET 4 study tested the hypothesis that rhythm control therapy, initiated early after the diagnosis of AF, may reduce the risk of adverse outcomes compared with the current practice of delayed transition to a rhythm control strategy. The project included 2789 patients with recent AF (diagnosed ≤1 year prior to enrollment) and comorbid cardiovascular conditions (age over 75 years, history of transient ischemic attack/stroke, or meeting two of the following criteria: age over 65 years, female gender, heart failure, arterial hypertension, diabetes, severe ischemic heart disease, stage 3 or 4 chronic kidney disease (glomerular filtration rate 15-59 ml per minute per 1.73 m2 of body surface area) and left ventricular hypertrophy (interventricular thickness septum to diastole >15 mm.) The median time after diagnosis of AF in registered patients was 36 days. Patients randomized to early rhythm control (ERC) received AADs (87% of cases) or AF CA (9% at baseline and 19% at 2 years of follow-up.) At a median follow-up of 5.1 years, the risk of the combined primary endpoint (sum adverse events - cardiovascular death, stroke, hospitalization due to worsening heart failure or acute coronary syndrome) was 21% lower (relative risk [RR] 0.79, 95% confidence interval [CI] 0.66-0, 94; p=0.005) due to a significant reduction in the risk of death from cardiovascular causes (RR 0.72, 95% CI 0.52-0.98) and stroke (RR 0.65, 95% CI 0.44-0.97) in the ERC group compared with the conventional treatment group [11]. More than 90% of the participants in EAST-AFNET 4 in both groups were constantly receiving anticoagulant therapy, so it can be assumed that it was the ERC strategy that provided improved cardiovascular outcomes in patients with AF. During the observation period, patients in the ERC group did not require an increase in hospital stay compared to the conventional treatment group.

It can be assumed that in the early stages, atrial remodeling can be reversible, but with prolonged existence of AF, it is less reversible or irreversible and only progresses. For this reason, the AFFIRM and RACE studies, which included patients with persistent AF and consistent significant left atrial structural and electrical remodeling, did not show significant differences in cardiovascular outcomes between VRC and rate control. In patients treated with EAST-AFNET 4 for ERC, the left atrium did not undergo the same degree of remodeling as in the conventional treatment group, which may have a positive effect on cardiovascular outcomes. At the same time, it should be considered that in this study, anticoagulants were continued during the ERC, while in the AFFIRM study, warfarin treatment could be stopped after 4 weeks of maintaining sinus rhythm, and in the VRC group, continuous anticoagulant therapy was prescribed by the protocol [5].

EAST-AFNET 4 Sub-Analyses

In a pre-planned sub-analysis of 798 EAST-AFNET 4 participants with New York Heart Association functional class II or III heart failure symptoms or left ventricular ejection fraction (LVEF) <50%, the effect of therapy was compared to ERC and conventional treatment on clinical outcomes. At a median follow-up of 5.1 years, there was a 26% reduction in the risk of events for the combined primary endpoint (cardiovascular death, stroke, hospitalization for worsening heart failure or acute coronary syndrome) (RR 0.74; 95% CI 0.56-0.97; p=0.03) in the RCR group versus the usual treatment group, regardless of the nature of the heart failure (p-interactions=0.63). The primary safety endpoint (death, stroke, or serious adverse events associated with rhythm control therapy) was recorded in 17.9% and 21.6% of cases in the ERC and usual treatment groups, respectively (RR 0.85; 95% CI 0.62 -1.17; p=0.33), and LVEF improved after 2 years in both groups by 5.3±11.6% and 4.9±11.6%, respectively (p=0.43).

Notably, IC class AADs were used for ERC in the majority (54%) of patients with preserved LVEF (≥50%; mean 61±6.3%), as well as in 26% of patients with moderately reduced LVEF (40-49%, on average 44±2.9%). According to the conclusion of the authors of the sub-analysis, the treatment strategy for ERC brings clinical benefit to patients with AF and signs or symptoms of heart failure [12].

Another pre-planned EAST-AFNET 4 analysis compared the effect of ERC therapy and VRC in oligosymptomatic and symptomatic patients with AF. Oligosymptomatic and symptomatic patients received similar therapy for rhythm control with equal frequency of CA, oral anticoagulants, and treatments for comorbid cardiovascular

disease. In patients with asymptomatic AF, the primary endpoint (combination of death from cardiovascular causes, stroke, or hospitalization with worsening heart failure or acute coronary syndrome) was 24% less common (RR 0.76; 95% CI 0.60-1, 03) in the ERC group compared with the VRC group, which is almost identical to the results of the study in symptomatic patients [13]. In addition, the risk of primary endpoint events was equally reduced in ERC in patients without AF symptoms, with mild or moderate symptoms, and with severe symptoms of arrhythmia (p interactions = 0.743). Current clinical practice guidelines limit the use of rhythm control therapy to patients with symptomatic AF. However, in EAST-AFNET 4, the clinical benefit of ERC did not differ between oligosymptomatic and symptomatic patients with AF, which may expand its use in practice.

The results of the EAST-AFNET 4 project, in addition to more frequent maintenance of sinus rhythm in the ERC group, could be affected by unintended differences in the provision of components of modern complex therapy for AF (taking anticoagulants, treating concomitant cardiovascular diseases, intensity of contacts between patients and investigators). A specially conducted analysis showed equal use of oral anticoagulants and an equal level of blood pressure during the entire observation period in the compared groups. The number of face-to-face visits of patients to research centers (2.13 per patient in the ERC group and 1.94 per patient in the usual treatment group; p<0.001) differed only because of the need to adjust anti-AADs therapy at the beginning of the study. Since the ERC and VRC groups practically did not differ in anything other than the study intervention, it may explain the benefits achieved in clinical outcomes with the first method of treating patients with AF [14].

Another pre-planned sub-analysis of the EAST-AFNET 4 study was devoted to assessing the impact on outcomes of the clinical form of AF: newly diagnosed (ND) (up to 7 days after the first clinical diagnosis of AF; n=1048), paroxysmal (n=994) and persistent (n=743). ERC reduced the risk of EAST-AFNET 4 combined primary efficacy endpoint events in all three forms of AF. However, in the ERC group, the risk of hospitalization for acute coronary syndrome was increased in ND AF (RR 1.50 at 95% CI 0.83–2.69; p-interaction = 0.032), although it decreased in paroxysmal (RR 0.64 at 95% CI 0.32-1.25) and persistent AF (RR 0.50 at 95% CI 0.25-1.00). Patients with ND AF spent more nights in the hospital (RR 1.38; 95% CI 1.12–1.70; p-interaction = 0.004) compared with patients with paroxysmal AF (RR 0.84; 95%, CI 0.67 -1.03) and persistent AF (RR 1.02 at 95% CI 0.80-1.30). ERC improved health-related quality of life (as assessed using the EQ-5D questionnaire) in patients with paroxysmal and persistent, but not with ND AF [15]. These unexpected, at first glance, results showed that patients with ND AF belong to a high-risk group, which is probably due to the cause of the onset of arrhythmia (acute heart failure, hypertensive crisis, hyperthyroidism, electrolyte disturbances, severe acute infectious disease, etc.). It is also important to remember that AF phenotypes overlap significantly, and patients can move from one phenotypic group to another, which makes the boundaries between different groups very arbitrary.

The results of therapy with the goal of ERC in EAST-AFNET 4 were compared in patients with AF and higher (CHA2DS2-VASc ≥4 points, n=1093) or lower (CHA_2DS_2-VASc <4 points, n=1696) burden of comorbidity. In the ERC group, the risk of the combined primary endpoint of the project effectiveness was reduced in patients with CHA_2DS_2-VASc ≥4 points (HR 0.64; 95% CI 0.51-0.81; p<0.001), but not with CHA_2DS_2-VASc <4 points (RR 0.93; 95% CI 0.73-1.19; p=0.56). According to the authors of this sub-analysis, in patients with newly diagnosed AF and more comorbidity, therapy for ERC effectively reduces the risk of adverse cardiovascular outcomes, while in patients with fewer comorbidities, the results of ERC may not be as favorable compared with conventional VRC [16]. In contrast, when using the Korean national database of routine clinical practice (n=54,216), it was shown that in patients who did not meet the inclusion criteria in EAST-AFNET 4 (mean age 54 years, median risk of thromboembolism according to CHA_2DS_2-VASc 1 point), ERC was also associated with a reduced risk of events in the primary efficacy endpoint (RR 0.80, 95% CI 0.66-0.97) [17].

Summarizing the data of the EAST-AFNET 4 study and its already available subanalyses, we can conclude that the ERC strategy should be considered as a new tool for the treatment of patients with AF, regardless of the symptoms of arrhythmia, the presence of chronic heart failure, and other comorbid pathologies. The results of the EAST-AFNET 4 study and its sub-analyses were not available for the preparation of the 2020 European AF guidelines. They conflicted with current guidelines for the standard of care for AF and showed an association between ERC and improved cardiovascular outcomes in patients with newly diagnosed arrhythmias compared with conventional therapy for rate control. The established improvement in outcomes may be associated with a decrease in the burden of arrhythmia, as well as with the preservation of the structure and function of the left atrium, moreover, the reverse development of remodeling of the left heart, which is associated with a decrease in the risk of cardiovascular complications of AF [18, 19]. Given these new ideas, the ERC strategy has obvious prospects for widespread use, since up to 80% of patients with newly diagnosed AF have reasons for such therapy [20, 21], and its benefits are observed in patients in real practice up to at least 75 years of age. [22]. Importantly, in several randomized controlled trials (AF-CHF, CASTLE-AF, ATHENA, EAST-AFNET 4) [11, 23-25], as well as a large observational project (n=31,220) based on the analysis of the national database The National Health Insurance Service (NHIS) of North Korea [26] confirmed the safety of rhythm control therapy in elderly patients with AF and comorbid cardiovascular diseases, which largely eliminated the concerns raised after the AFFIRM study [27].

It goes without saying, some patients are not suitable for a sinus rhythm control strategy, and sometimes even for an initial attempt to restore it. Among them are patients with genetically determined AF and a very long history of asymptomatic arrhythmia, for whom there is little evidence of the clinical benefit of a rhythm control strategy [28]; patients with severe atrial cardiomyopathy and severe atri-

al dilatation [29]; abandoned rhythm control; patients with short life expectancy and very old people for whom limited data are available.

POSSIBLE METHODS FOR CARRYING OUT THE STRATEGY FOR SINUS RATE CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

Cardioversion is an important component of a rhythm control strategy, although not a means of maintaining a rhythm as such, it usually represents a transitional step to taking AADs or CA AF to achieve a long-term effect. The domestic class III AAD niferidil (Refralon®) makes it possible to successfully solve the problem of restoring sinus rhythm in approximately 90% of patients with persistent AF, i.e., it is a real alternative to electrical cardioversion [30].

Concerns about the safety of anti-relapse treatment of AF with AADs have developed historically, supported by the results of the AFFIRM and RACE studies [5, 6]. In AFFIRM, 63% of patients randomized to rhythm control were treated with amiodarone, and the small excess mortality in this group was entirely non-cardiovascular, primarily attributable to lung disease and cancer associated with chronic amiodarone use [27]. The results of early comparative studies of rhythm control and VRC could be affected by less advanced treatment regimens using inadequately high or suboptimal doses of AADs, potentially provoking proarrhythmia or reducing the effectiveness of treatment, the participation of patients with a long history of AF, insufficiently strict monitoring, inadequate anticoagulant therapy [31].

Dronedarone, which differs from amiodarone in the absence of two iodine atoms in the molecule and the presence of a methylsulfonamide group, in a large randomized ATHENA study involving 4628 patients with AF and additional risk factors for death, reduced the risk of the sum of adverse events (hospitalization for a cardiovascular reason or death) by 24%. compared with placebo (RR 0.76; 95% CI 0.69-0.84; p<0.001), which contributed to optimism about this anti-anxiety drug [25]. However, the PALLAS randomized trial of dronedarone in patients with persistent AF and risk factors for cardiovascular complications was soon stopped for safety reasons [32]. After enrollment of 3236 patients, dronedarone increased the risk of primary combined endpoint events (stroke, myocardial infarction, systemic embolism, or death from cardiovascular causes) (RR 2.29; 95% CI 1.34-3.94; p = 0.002), death from cardiovascular causes (RR 2.11; 95% CI 1.00-4.49; p=0.046), death from arrhythmia (RR 3.26; 95% CI 1.06-10.00; p=0.03), stroke (RR 2.32, 95% CI 1.11–4.88; p=0.02), hospitalization for heart failure (RR 1.81, 95% CI 1.10– 2.99; p=0.02) compared with placebo. These negative results were followed by recommendations from the Food and Drug Administration and the European Medicines Agency to limit the use of dronedarone in AF.

Subsequently, practitioners did not receive new AADs to control sinus rhythm in patients with AF. Enthusiasm for the development of AADs has been dampened by many factors, including stringent regulatory requirements, as well as historical experience of limited efficacy and risk of cardiac/extracardiac side effects. The pharmaceutical industry offers limited hope for progress anytime soon. Only rare innovations are proposed outside the already known areas, including beta-blockers, blockers of K+ channels of cell membranes, modulators of Ca2+ processing in cardiomyocytes, antioxidants or parasympatholytics [33].

Despite this, AADs continue to play a dominant role in the global clinical practice of antiarrhythmic treatment, and, for example, in the EAST-AFNET 4 study in the rhythm control group, 92% of patients with AF initially underwent antiarrhythmic drug therapy [11].

CA, as a rule, isolation of the pulmonary vein orifices, is superior to AADs in the effectiveness of rhythm control in patients with AF [34]. However, CA cannot completely eliminate the recurrence of this arrhythmia - the rate of successful rhythm control approaches 80% in paroxysmal and is about 60% in persistent AF [35], and repeated procedures are required in 20-50% of patients [36]. At the same time, there is concern about the deterioration of the reservoir, pumping, and conduction functions of the left atrium as a result of the damaging effect of CA on the tissue of the left atrium, the long-term consequences of which are unknown [37].

The CABANA study, which compared the effectiveness of interventional and medical rhythm control in patients with AF, confirmed the greater effectiveness of CA in reducing the risk of arrhythmia recurrence (RR 0.52, 95% CI 0.45-0.60), but the event rate of the combined primary endpoint (death, disabling stroke, major bleeding, or sudden cardiac arrest) did not differ between groups, 8.0% and 9.2%, respectively (p = 0.30) [38]. Periprocedural complications were observed in 4.8% of patients randomized to the CA group and included pericardial tamponade (0.8%), hematomas (2.3%), and pseudoaneurysms (1.1%). In the antiarrhythmic drug therapy group, proarrhythmia was recorded in 0.8% of patients, which is significantly less than in a similar group of AFFIRM participants (2.5%) [5] and indicates improvements in approaches to the use of available AADs over the past two decades.

In the EARLY-AF (n=303) and STOP AF (n=203) trials, participants with symptomatic untreated paroxysmal AF were randomized to cryoballoon CA (CBA) or antiarrhythmic drug therapy, respectively [34, 39]. After 1 year of follow-up with an implanted cardiac monitor in the EARLY-AF study, the recurrence rate of atrial tachyarrhythmia was 42.9% and 67.8% in patients who were prescribed CBA or AADs, respectively [34]. In the STOP AF study, 74.6% and 45.0% of patients in the CBA and drug therapy groups did not have recurrent atrial tachyarrhythmias [39]. The presented studies showed the benefits of CBA in influencing secondary endpoints but did not have sufficient statistical power to demonstrate the superiority of the procedure compared to AADs in relation to the most important adverse outcomes of AF (death, stroke, heart failure).

The two most common CA methods, radiofrequency ablation and cryoablation, appear to be comparable in terms of efficacy in preventing recurrence of AF without statistically significant differences in complication rates [40,41]. In general, CA can be a first-line therapy for paroxysmal (recommendation class IIa) and persistent AF (recommendation class IIb) [3], but these provisions have a few limitations [42]. CA carries the risk of serious com-

plications of the intervention (eg, intraprocedural stroke, pulmonary venous stenosis) [43] in the absence of strong evidence for improved prognosis [38]. Successful CA studies have involved centers with more experience and a staff of highly qualified professionals, but in real practice, less experienced doctors can perform ablation with less efficiency and safety. Carefully selected patients were included in the AF CA studies, which may have influenced the results obtained. An example is the CASTLE-AF study, which compared CA (n=179) with medical therapy (AAD or means of VRC, n=184) in patients with paroxysmal or persistent AF and chronic heart failure with an LVEF ≤35%. The composite primary endpoint (death from any cause or hospitalization due to exacerbation of heart failure) was recorded in significantly fewer patients in the CA group than in the drug group (RR 0.62; 95% CI 0.43-0.87; p=0.007) [44]. The selection of patients in CASTLE-AF was so thorough (on average, only 1 patient per year out of 10 screened during this time was registered in each center) that there were reasonable doubts about the reproducibility of positive study results with widespread use of AF CA [45]. The quality of the analysis of the data obtained in this work was also subjected to serious criticism [46]. At the same time, CASTLE-AF is the only randomized trial that showed a reduction in the risk of death and hospitalization for heart failure, on the results of which the recommendations (in the European document of class IIa, in the American - IIb) are based on the use of CA in the combination of AF and heart failure [3, 7].

Rhythm control is a long-term strategy for the treatment of AF and usually requires different treatment options at different stages. They may suggest referral to AF CA when antiarrhythmic agents are ineffective, to recurrent AF CA, or to treatment with AADs after AF ablation for recurrent arrhythmias [47]. In patients with atrial fibrillation, CA and AADs appear to have a synergistic effect, that is, when used together, they sharply increase the likelihood of maintaining sinus rhythm [47-49]. Surgery for AF may be successful in selected patients in whom other options for rhythm control have failed [50]. Atrioventicular node-directed therapies such as beta-blockers, verapamil/diltiazem, digitalis preparations, or ablation/pacing play an important role in patients with persistent AF and/or severe arrhythmia burden. But an attempt to restore sinus rhythm should be considered in many of these patients [51].

Choosing a rhythm control strategy, it is very likely that reducing the burden of AF will provide the expected beneficial effect of treatment on clinical outcomes [52], therefore, for long-term anti-relapse therapy, it is advisable to use the most effective anti-organotoxic anti-inflammatory drugs with or without CA. The last provision, based on the priority of safety, casts doubt on the leading role of amiodarone in the long-term treatment of AF [53]. Amiodarone is recommended for long-term rhythm control in patients with atrial fibrillation, including chronic heart failure with decreased LVEF, but due to its extracardiac toxicity, other antiarrhythmic drugs should be considered first, if possible (recommendation class I) [3]. At the same time, in patients with heart failure, the choice of AADs is limited to amiodarone.

In the absence of appropriate randomized trials, the results of the large TREAT-AF project, which retrospectively compared the outcomes of treatment of newly diagnosed AF with class IC (n=3973) or class III (n=6909) AADs, are of interest. At a median follow-up of 4.9 years, IC class AADs therapy was associated with a lower risk of hospitalization for AF (RR 0.77 at 95% CI 0.73-0.81), cardiovascular disease (RR 0.78 at 95% CI 0.75-0.81) or heart failure (RR 0.70, 95% CI 0.64-0.76) and a lower rate of ischemic stroke (RR 0.74, 95% CI 0.65-0, 85) compared with class III AAD therapy [54].

Of the IC class AADs available in our country (allapinin, propafenone, etacizin), only when using the first one, the development of dangerous ventricular proarrhythmia during the treatment of AF was not reported. The creation in the Russian Federation of a new dosage form of lappaconitine hydrobromide - Allaforte® (long-acting tablets of 25 mg and 50 mg with a slow release of the active substance) led to a pronounced decrease in the frequency of its neurological side effects. A pharmacokinetic study showed a significant prolongation of the half-life of lappaconitin after taking Allaforte®, which allows to reduce the frequency of its administration compared to other class IC AADs and increase patient adherence to treatment [55].

CONCLUSION

For almost 20 years, there has been and is reflected in clinical practice a controversial notion of the equivalence of the effect of AF therapy for rhythm control or VRC on cardiovascular outcomes. During this time, the overall safety of AF treatment for rhythm control and anticoagulant therapy has improved. Recently, a rhythm control strategy has been shown to reduce the risk of adverse cardiovascular events compared with standard rate control in patients with newly (up to 1 year) diagnosed AF. ERC significantly reduced the risk of death from cardiovascular causes and stroke compared with VRC. In most patients with newly diagnosed AF, it is time to consider a promising therapeutic option, including ERC in combination with the use of oral anticoagulants, taking into account the risk of stroke, diagnosis and treatment of comorbid cardiovascular diseases and risk factors. This approach may reduce the risk of adverse outcomes (cardiovascular death, stroke, heart failure, hospitalization), reduce symptoms and improve the quality of life of patients with AF.

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