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LEADING ARTICLE

Antiarrhythmic therapy in patients with paroxysmal and persistent atrial fibrillation: prediction and prevention of progression to permanent form of arrhythmia

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Summary

A realistic objective for treatment of patients with paroxysmal and persistent atrial fibrillation (AF) should be to prevent its progression to a permanent form of arrhythmia, which is associated with an increased risk of complications and worsening prognosis. This review presents easily identifiable predictors of AF progression, reviews available treatment options, and their efficacy and safety. Early and active measures to restore and maintain sinus rhythm by pharmacological and non-drug methods will prevent the development of arrhythmia substrate; inhibit the progression from paroxysmal to permanent AF, with potentially beneficial effects on prognosis.

Keywords

Atrial fibrillation, progression, treatment

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Between 1990 and 2010, the prevalence of AF worldwide, and its associated morbidity and mortality, increased about two times despite the best efforts of medical science and health care [1]. According to epidemiological studies conducted in Western Europe, AF is already detected in 2.0–4.7% of cases in the general population [2]. According to forecasts, by 2050 the number of patients with AF may increase more than two times [3]. AF is a major cause of stroke and congestive heart failure (HF). Even in AF patients under the age of 65 years without concomitant diseases, there is a two-fold increase in mortality compared with general population [4].

In six randomized clinical trials (PIAF, AFFIRM, RACE, STAF, HOT CAFÉ, AF CHF), treatment strategies in AF patients to restore and maintain sinus rhythm did not reduce mortality compared with the tactics of shortening the ventricular rate while maintaining AF. This result is associated with a lack of efficacy and safety of modern anti-arrhythmic drugs, and with the limitations of design of research studies [5]. In those studies, elderly patients with late-stage development of an AF substrate in atria and considerable stability arrhythmia were included. Meanwhile, even in those studies a decrease in symptoms and improvement in quality of life has been convincingly demonstrated while maintaining sinus rhythm, as well as a significant reduction in total mortality by 47% (P<0.0001) in the actual maintenance of normal sinus rhythm during observation period [6].

In general, the results of AF treatment are far from desired, which is often attributed to an inadequate understanding of the mechanisms of its development. At the same time, cellular and molecular mechanisms of AF initiation have been well studied [7]. It has been established that aging, hypertension, valve disease, HF, myocardial infarction, obesity, smoking, diabetes, thyroid dysfunction and intense physical endurance training contribute to structural remodeling of the atria [8]. With regard to clinical practice, special attention is drawn to the concept of AF progression from paroxysmal to a permanent clinical form [9].

Paroxysmal AF may take up to 7 days, but differs by spontaneous termination, usually within the first 48 hours. In paroxysmal AF lasting more than 48 hours, the probability of spontaneous termination of arrhythmia is low, but the risk of systemic thromboembolism significantly increases, which requires consideration of initiating antithrombotic therapy. Persistent AF, unlike paroxysmal, does not stop by itself, continues for more than 7 days, and medication or electrical cardioversion may be useful in resolving the problem. Prolonged persistent AF is diagnosed when AF continues for a year or more, and the strategy of sinus rhythm restoration and conservation using anti-arrhythmic drugs and/or ablation in the left atrium are chosen. Permanent AF is diagnosed in cases when a patient and a doctor consider possible to preserve arrhythmia, or when previous attempts of cardioversion or cardiac surgery treatments have been unsuccessful [10,11].

In recent years, antithrombotic therapy in patients with AF has become the most popular, which actually changes the prognosis for patients. It is emphasized that the risk of stroke depends not on the form of AF (paroxysmal, persistent or permanent), but on other clinical factors, summarized by scales, $CHADS_2$ and more modern CHA_2DS_2-VASc, designed to assess stroke risk [10,11]. Indeed, according to the ACTIVE W study, the incidence of stroke in patients with paroxysmal (n=1,202, the average score $CHADS_2$ 1.79±1.03), persistent and permanent AF (n=5,495, the average score $CHADS_2$ 2.04±1.12, P <0.00001) was not significantly different (P=0.496), even after adjusting for baseline clinical differences (P=0.755) [12]. One might think that in paroxysmal AF a shorter period of blood stagnation in the atria during fibrillation takes place, but the rapid restoration of mechanical atrial systole contributes to dislocation of fresh blood clots into the arterial system. In persistent/permanent AF, long/continuous stagnation of blood in the atria creates a constant environment for thrombus formation in the atria, but long-term/permanent absence of mechanical atrial systole allows blood clots to organize, to grow together with the wall of the atrium and even dissolve by the fibrinolytic system in the body.

However, in a large modern study, ARISTOTLE, the frequency of stroke or systemic embolism was significantly higher in patients with persistent or permanent AF (n=15,412) than in patients with paroxysmal AF (n=2,786) (1.52% vs. 0.98%, P=0.003, adjusted for baseline clinical differences P=0.015). There was also a tendency towards higher mortality in patients with persistent or permanent AF (3.90% vs. 2.81%, P= 0.0002, adjusted P=0.066) [13].

K. Imai *et al*. [14] recently developed and tested a scale assessing the risk of severe HF in New York Heart Association (NYHA) functional class III or IV patients with non-valvular AF – ARC2H. According to this scale, a patient gains 1 point if he/she is 72 years and older, has heart rate of 80 beats per minute or more, hypertension, and he/she gains 2 points if there is previously established HF.

The annual risk of severe HF ranged from 0.8% to 35% in patients with 0 and 5.4 points according to ARC2H, respectively. In the largest study, AFFIRM, which compared the tactics of restoring and maintaining sinus rhythm with the tactics of shortening of ventricular rate while maintaining AF, the long duration of AF was directly related to the high prevalence of symptoms of chronic HF [15].

According to S. Taillandier et al. [16], among 1,906 patients with a combination of AF and chronic HF, 55% of patients had persistent or paroxysmal and 45% – permanent form of arrhythmia. During an about 1.9 years of follow-up, the risk of hospitalization for decompensation of HF was significantly higher in patients with permanent AF, especially in a subgroup of individuals with preserved left ventricular ejection fraction.

The presented data confirm the known position [17] – slowing the progression of AF to its more prolonged forms may be considered as one of the goals of its therapy that can mitigate a risk of thromboembolism, HF and mortality. Modern ideas about the factors of such AF progression necessarily include structural and electrical remodeling of the atria. Sustained AF can cause an inflammatory reaction that leads to activation of myofibroblasts and the release of cytokines, such as transforming growth factor-ß and platelet-derived growth factor, and also profibrotic proteins. Activation of signaling cascades involving the latter is essential for the development of fibrosis. It leads to dysfunction of ion channels, apoptosis of cardiomyocytes and growth of extracellular matrix, which contributes to both electric and structural remodeling – the basis for preservation of AF [18,19].

Studies of modern pharmacological types of treatment of underlying disease (upstream therapies) to prevent electric (blockers of slow calcium channels) and structural remodeling, fibrosis (renin-angiotensin system blockers, statins, omega-3 fatty acids), revealed contradictory, mostly negative results [20,21]. Despite this, one of the objectives of treating AF patients should be regression of left ventricular hypertrophy. Multivariate data analysis of the AFFIRM project has shown that thickening of the left ventricular wall, especially the interventricular septum, is an independent predictor for overall mortality (1.46 relative risk (RR), 95% confidence interval (CI), from 1.14 to 1.86, *P*=0.003) and stroke (1.89 RR, 95% CI, from 1.17 to 3.08, *P*=0.01). Concentric left ventricular hypertrophy was associated with the highest overall mortality (1.53 RR, 95% CI, from 1.11 to 2.12, *P*=0.009) [22]. It is known that the presence of left ventricular hypertrophy increases the risk of death because of ventricular tachyarrhythmia, including instigated antiarrhythmic therapy.

Moreover, left ventricular hypertrophy predisposes to the resumption of AF during a therapy to maintain sinus rhythm. In a cohort of 1,088 participants of the AFFIRM study, the median time of AF recurrence in patients with concentric left ventricular hypertrophy was 13.3 months (95% CI, from 8.2 to 24.5) versus 28.3 months (95% CI, from 20.2 to 48.6) in patients without hypertrophy. Concentric type of hypertrophy was an independent predictor of AF recurrence (1.49 RR, 95% CI, from 1.10 to 2.01, *P*=0.01) [23].

R. Chung *et al*. [24] selected 537 AF patients with left ventricular hypertrophy where the wall thickness ≥1.4 cm (mean age 67.5±11.7 years, left ventricular ejection fraction (LVEF) 48.3±13.3%), some not receiving antiarrhythmic drugs and some receiving amiodarone or other antiarrhythmic agents to maintain sinus rhythm. Amiodarone therapy was associated with lower survival (*P*=0.001), even after age adjustment, LVEF and the presence of coronary artery disease (CAD) (*P*=0.023). These data do not support expert opinion that treatment of persistent AF in patients with left ventricular hypertrophy should be conducted with amiodarone due to the fact that, compared to it, other antiarrhythmic drugs increase mortality [25].

According the Euro Heart Survey registry [26] and J-RHYTHM II study [27], within one year 10–15% of patients have progression from paroxysmal to persistent AF. It is shown that old age, organic heart disease, hypertension, AF lasting more than 3 months, tactics of shortening ventricular rate contribute to progression to more sustainable forms of AF, but restoration and maintenance of sinus rhythm, left atrial dilatation and obesity do not [28]. Also, the HATCH score was suggested, according to which a patient gets 2 points for the presence of HF and history of transient ischemic attack / stroke, and 1 point for the age over 75 years, hypertension, chronic obstructive pulmonary disease [17]. If the total score is from 5 to 7 the risk of progression from paroxysmal to persistent AF on the background of a drug therapy can reach 35–50%, and at 0 points – about 6%.

It is important to note that psychological status of AF patients deteriorates as arrhythmia progresses. In a study conducted by A.F. von Eisenhart Rothe *et al*. [29], after eliminating the influence of gender, age and other relevant factors, major depressive disorder occurred 44% more often (*P*=0.007) at persistent AF compared to paroxysmal.

Antiarrhythmic drugs, despite their well-known shortcomings, remain the only widely available means for the effective suppression of AF, i.e. implementation of tactics of maintaining sinus rhythm. Are they able to slow the progression of this arrhythmia to its permanent form? In AF patients with maintaining sinus rhythm, the left atrium decreases in size and left ventricular systolic function improves. Both of these indicators are important factors associated with progression of AF [30]. However, in a study conducted by S.B.de Vos *et al.* [31], only class IC antiarrhythmic medications significantly (P=0.0013) inhibited the progression of AF during a year of observation.

The most dangerous, though rare, side effect of class I drugs is a ventricular tachyarrhythmia. Its harbinger is an expansion of the QRS complex on the electrocardiogram (ECG). In the AFFIRM study, to maintain sinus rhythm it was allowed to use drugs of class IA (disopyramide, procainamide, quinidine) and class IC (moricizine, propafenone, flecainide). The QRS duration ⩾120 ms was associated with a significant (1.61 RR, 95% CI, from 1.29 to 2.03, P<0.001) increase in the risk of death (all-cause, cardiovascular and arrhythmic) and hospitalization (1.14 RR, 95% CI, from 1.07 to 1.34, P=0.043). Increased mortality (P=0.03) was also observed among patients with QRS duration 90–119 ms and concomitant HF [32].

These recently published data require consideration when choosing between available in Russian class IC antiarrhythmic drugs allapinin, propafenone and etatsizin. When used in normal dosages allapinin the least expands the QRS complex, which ensures the highest safety of therapy, but does not at least inferior to propafenone and etatsizin efficiency. According to our data, in comparable groups of patients with highly symptomatic persistent AF (Table 1), allapinin in dose of 67±12 mg/day caused widening of the QRS complex by 14% in average, propafenone – 385±44 mg/day – 19%, and etatsizin – 126±20 mg/day – 23%, respectively.

To prevent such side-effect of class IC antiarrhythmic drugs as atrial flutter with a high frequency of impulses to the ventricles, to achieve a therapy of high anti-relapse activity for AF even at lower doses of drugs it is appropriate to take them in combination with sotalol or amiodarone [33]. According to the latest data of the PREFER registry [34], in 461 centers of 7 European countries frequently AF patients, in order to maintain sinus rhythm, are assigned amiodarone (24.1% of cases), flecainide or propafenone (13.5%), sotalol (5.5%), and dronedarone (only 4.0%, respectively). Similar statistics from 9 European countries was presented by the authors of the EORP-AF registry [35]. Before starting treatment with amiodarone and every 6–12 months of therapy, it is required to monitor the lungs, liver and thyroid. The ORBIT-AF registry in the US [36] showed that among 10,061 AF patients, the majority of them (often elderly people with hypertension, HF, previous stroke, and minimally symptomatic arrhythmias) received therapy which slows down the ventricular rate. Of course, this treatment strategy does not provide reverse remodeling of the heart and enhances morphological changes in the atria that perpetuate the arrhythmia [37].

Currently, the EAST study, in order to prevent stroke and other adverse events by early therapy of preserving sinus rhythm, includes patients with newly emerging AF and a CHA2DS2-VASc score of 2 or more [38]. It is assumed that preservation of sinus rhythm from the early detection of AF will keep the structure and function of the atria more effectively than the standard treatment (transition to the restoring and maintaining sinus rhythm in case of continued symptoms with effective reduction of ventricular contractions on the background of AF). The EAST project suggests using not only antiarrhythmic drug therapy of AF, but also catheter ablation in the left atrium.

In 2012, two authoritative expert groups expanded indications for radiofrequency catheter ablation to maintain sinus rhythm in patients with AF [25,39].

Table 1. **Baseline characteristics of patients with persistent AF**

Parameter	Allapinin (n=28)	propafenone (n=24)	Etatsizin (n=25)
Age, years, (M±m)	59.5±5.3	57.7±4.8	56.8±4.9
Men/Women	14/14	11/13	13/12
Hypertension,%	78.6%	83.3%	76.0%
Idiopathic AF, %	10.7%	4.6%	12.0%
CAD,%	10.7%	12.5%	12.0%
Functional class of chronic HF, (M±m)	1.50±0.33	1.43±0.26	1.58±0.29
Anteroposterior diameter of the left atrium, mm (M±m)	43.6±2.1	44.2±2.3	43.8±2.0
LVEF, % (M±m)	60.5±4.2	58.6±3.8	62.1±4.5

Recently, the first results of the multicenter, prospective, randomized SARA study of 146 patients with persistent AF were published, it established the superiority of catheter ablation in the maintenance of sinus rhythm compared with antiarrhythmic drug therapy. From 3 to 12 months after initiation of the therapy, there were no records of episodes of AF or atrial flutter lasting more than 24 hours in 70.4% of patients who underwent ablation, and in 43.7% of patients treated with class IC or III antiarrhythmic drugs (P=0.002) [40].

Regression of dilatation and remodeling of the left atrium was observed in AF patients after catheter isolation of pulmonary veins [41]. As a result of sinus rhythm restoration and maintenance, initially decreased LVEF significantly increases, exercise tolerance and quality of life improves compared with the tactics of shortening of ventricular rate while maintaining AF [42,43].

Despite these positive data directly indicating preferred tactics of sinus rhythm control, the left atrial catheter ablation in terms of its implementation requires further research [44]. It is still carefully studied and evaluated the frequency of such immediate complications of this invasive procedure as pericardial effusion, cardiac tamponade, pulmonary vein stenosis, ulcers or esophageal perforation with the atrio-esophageal fistula formation, stroke/transient ischemic attack, phrenic nerve injury, arteriovenous fistula in a puncture on the hip [45].

No one denied the presumption of a possible deterioration of atrial function in years after ablation. H. Cochet *et al*. [46] studied the structure and function of the left atrium in 26 patients with persistent AF 80±15 months after radiofrequency catheter ablation. According to magnetic resonance imaging (MRI), contractility and compliance of the left atrium noticeably deteriorated after 5 years of successful ablation of persistent AF in direct relation to scar size.

Radiofrequency catheter ablation appears to be the most appropriate in paroxysmal AF. Observation of 889 patients with paroxysmal or persistent/long-lasting persistent AF for an average of 64 months after catheter ablation in the left atrium (pulmonary vein isolation and linear effects) showed an early advantage of such procedure. AF progression to its permanent form was significantly more frequently observed in patients with persistent (10%) or long-lasting persistent AF (14.6%) than in patients with paroxysmal AF (2.7%, P<0.001) [47].

The ongoing big CABANA and EAST projects will help in the future answer the remaining questions, including the long-term efficacy of catheter ablation and the impact of the underlying disease on treatment outcomes.

During open heart surgery, some surgical effects can be performed on the atria to eliminate AF. According to the results of 7 comparative studies of surgical ablation on the epicardial surface and radiofrequency ablation on the endocardial surface of the left atrium, the first procedure usually eliminates AF during a year (74% versus 43% of patients; 3.91 RR, 95% CI, from 2.38 to 6.42, P<0.00001). However, the surgical ablation often required pacemaker implantation, and the number of neurological complications and cardiac tamponade appeared to be comparable to those in the group of catheter ablation [48].

A tolerant attitude toward asymptomatic AF is erroneous. K.Senoo *et al*. [49] observed 1,176 patients with paroxysmal AF in average for 1,213±905 days, noting the progress of arrhythmia toward its permanent form with a frequency of 6% per year. In 468 asymptomatic, at the first examination, patients, even at low levels of risk, a more frequent progression of AF was noted compared to patients who had arrhythmia symptoms. This paradoxical result, according to the authors, is due to less intensive drug treatment and rare use of radiofrequency ablation to maintain sinus rhythm.

Management of the known risk factors may also be useful. According to a 16-year observation of 34,720 female participants in the Women's Health Study project who did not initially have AF and cardiovascular disease, obesity and elevated levels of hemoglobin A1c contribute to the occurrence of persistent and permanent AF. It is expected that reduction of overweight and glycemic control can reduce the proportion of people with persistent AF [50].

Conclusion

Large clinical investigations have not yet shown prognostic benefits of rhythm control compared with ventricular rate control during persistent AF, but they included patients in the late stages of the disease. It is likely that only intervention at an early stage of AF progression will be more effective. Early and active measures to detect AF, restoration and maintenance of sinus rhythm by pharmacological and non-drug methods will prevent the development of arrhythmia substrate, inhibit the progression from paroxysmal to persistent AF with potentially beneficial effects on prognosis. Therefore, for relatively young patients and/or for patients with severe symptoms of AF, restoration and maintenance of sinus rhythm is preferred.

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