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Antiarrhythmic drug therapy after atrial fibrillation ablation: data of the ESC-EHRA registry

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Aim. Catheter ablation (CA) is an effective approach for rhythm control in atrial fibrillation (AF), however antiarrhythmic therapy (AAT) remains important. There is a lack of data about long-term AAT use after CA. This study evaluates AAT after CA for AF.

Material and methods. In 2012-2016, EURObservational Research Programme of Atrial Fibrillation Ablation Long-Term (EORP AFA L-T) registry was conducted, which included 476 Russian patients (57,1% — men; mean age — 57,1±8,7 years). The follow-up after CA was 12 months (available in 81,9% of patients). The use of AAT was evaluated prior to hospitalization, during hospitalization for CA, as well as at 3, 6 and 12 months of follow-up.

Results. Prior to CA, 439 (92,2%) patients received AAT. During CA, 459 (96,4%) patients were treated with AAT. After CA, AAT was used by 463 (97,3%), 370 (94,8%), and 307 (78,7%) patients at 3, 6 and 12 months of follow-up, respectively. There was no arrhythmia recurrence in 187 (47,9%) subjects. Among these patients, 40 (21,4%) received class IC or III AAT. The peak of AAT use was found for class IC agents within 3 months after CA (P<0,05), while for other drugs this trend was not observed. There were no factors associated with AAT usage in patients without arrhythmia recurrence after CA. A positive correlation of arrhythmia non-recurrence with a minimum number of previously used antiarrhythmic agents was revealed (RR=0,85; 95% CI 0,73-0,98; P=0,03).

Conclusion. The frequency of AAT use after AF ablation is significantly reduced. However, there is a cohort of patients without documented arrhythmia recurrence still receiving AAT, which requires special attention of physicians. There were no clinical predictors of continued AAT in subjects without arrhythmia recurrence.

Key words: atrial fibrillation, antiarrhythmic therapy, registry, catheter ablation.

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Atrial fibrillation (AF) is the most common sustainable arrhythmia in clinical practice. The complex therapy of AF includes the prevention of thromboembolic events, conservative and interventional treatment aimed at improving the rhythm and preventing the AF recurrence. A number of randomized clinical trials [1-4] showed that pulmonary vein isolation was more effective than antiarrhythmic therapy (AAT) in rhythm control. AAT remains an important component of AF treatment in most patients, both aimed at catheter ablation and those who do not have indications for interventional treatment.

Earlier studies have shown that a history of AAT before catheter ablation can be a predictor of cardiac ablation outcomes [5]. At the same time, according to expert opinion and official guidelines [6, 7], in the first 3 months after ablation, AAT is indicated for the prevention of early recurrence of AF. The decision to continue therapy is based on AF recurrence, as well as the individual characteristics of a patient [8].

The clinical guidelines indicate AAT withdrawal after catheter ablation if there is no documented AF recurrence. However, in actual practice, the frequency of AAT use after ablation, the type of preferred AAT and its duration remain unstudied.

To obtain relevant data on catheter ablation (CA) for AF in 2012-2016, a registry observational study was conducted on the management of patients hospitalized for CA (EORP Atrial fibrillation ablation long-term registry = EORP AFA LT). As a part of the Russian Society of Cardiology, data from 13 hospitals of Russia were included in the study.

The aim of this study was to assess the characteristics and changes of AAT in the preoperative, perioperative and long-term periods after AF ablation in Russia.

Material and methods

Registry. The EORP AFA L-T registry was a prospective international multicenter project. The registry organizers did not provide for specific prescriptions for drug therapy and diagnostic procedures for patients. It was carried out according to current guidelines and local clinical practice.

The inclusion criteria were the age >18 years and hospitalization for AF ablation.

The registry included data from 106 cardiology centers from 27 countries, including 13 Russian institutions.

In total, 3742 patients were included in the registry, of which 476 were Russian patients (study group). The main clinical characteristics of patients were presented in a previous publication [9].

Catheter ablation and follow-up. AF ablation included pulmonary vein isolation. At the discretion of the operator, an additional substrate modification was performed in the left and/or right atrium.

After AF ablation, patients were monitored for 12 months with rhythm control and in-person recurrence

Table 1

Applied dosages of AAT

	Ic			III	
	Propaphenone	Lappaconitine hydrobromide (Allapinin)	Ethacyzin	Amiodarone	Sotalol
Dosages (mg/day)	150-600 (450)	25-160 (75)	100	100-600 (200)	40-640 (160)

Note: the ranges of prescribed dosages and the median daily dose in brackets for the entire observation period are indicated. The protocol of the register did not provide for the separation of the beta blockers and CCB groups by individual drugs.

Table 2

The frequency of using various AAT during the follow-up period

	Before hospitalization (476 subjects in total)	During hospitalization for AF CA (476 subjects in total)	3-month follow-up period (476 subjects in total)	6-month follow-up period (390 subjects in total)	12-month follow-up period (390 subjects in total)
Number of patients received AAT	439 (92,2%)*	459 (96,4%)	463 (97,3%)	370 (94,8%)*	307 (78,7%)*
Ic	134 (28,2%)	145 (30,3%)	148 (31,1%)	112 (28,7%)	27 (6,9%)*
• Propaphenone	94 (19,7%)	104(21,8%)	106 (22,3%)	79 (20,3%)	26 (6,7%)*
• Allapinin	37 (7,8%)	40 (8,4%)	41 (8,6%)	31 (7,9%)	0*
• Etatsizin	3	1	1	2	1
III	254 (53,3%)	297 (62,4%)*	298 (62,6%)	237 (60,8%)	130 (33,3%)*
• Amiodarone	156 (32,8%)	172 (36,1%)	167 (35,1%)	135 (34,6%)	49 (12,6%)*
• Sotalol	97 (20,6%)	124 (26,1%)*	130 (27,3%)	102 (26,2%)	81 (20,8%)
beta-blockers	217 (45,6%)	199 (41,8%)	183 (38,4%)	176 (45,1%)*	180 (46,2%)
CCB	43 (9%)	49 (10,3%)	42 (8,8%)	36 (9,2%)	36 (9,2%)
Ic+III	23 (4,8%)	28 (5,9%)	23 (4,8%)	18 (4,6%)	1 (0,3%)*

Note: * — P<0,05.

Abbreviations: AAT — antiarrhythmic therapy, CA — catheter ablation, AF — atrial fibrillation, CCB — non-dihydropyridine calcium channel blockers.

detection (surface ECG, Holter monitoring), by telephone or using implantable monitors. Recurrence was considered to be any documented episodes of atrial tachyarrhythmia lasting more than 30 seconds.

The exclusion criterion was feedback failure until the end of the follow-up period.

The primary endpoint was the AAT frequency in patients on follow-up visits at 3, 6, and 12 months.

Secondary endpoints were the change or continuation of AAT, the AAT continuation for 12 months in patients without AF recurrence.

Clinical indicators and accepted therapy were entered into the electronic database before hospitalization, during hospitalization for AF ablation, immediately after CA, after a 3-month (blinded) period and at a 12-month visit; if necessary, unscheduled visits were carried out and taken into account.

In the early postoperative period, complications of AF ablation were evaluated.

Antiarrhythmic therapy. The electronic database included data on the intake of a wide range of drugs for the treatment of cardiovascular diseases, including AAT, therapy for hypertension (HTN), hypercholesterolemia, heart failure, as well as anticoagulant therapy. AAT was carried out using class IC (Propafenone, Lappaconitine hydrobromide (Allapinin), Diethylaminopropionylethoxycarbonylaminophenothiazine (Etatsizin)) and class III (Amiodarone, Sotalol) antiarrhythmic agents, as well as beta blockers and non-dihydropyridine calcium channel blocker (CCB). The applied dosages of class IC and III agents are shown in Table 1. The drugs were prescribed by physician caring for patient.

Statistical analysis. Continuous variables are presented as mean±standard deviation. Frequencies are presented as a percentage of the absolute number. The relationship was assessed using a Pearson correlation coefficient for a normal distribution and Spearman's correlation coefficient for non-normal distribution. To compare the normally distributed mean values, we used Student's t-test, while for non-normally distributed values — Mann-Whitney U test. For frequency comparison, the Pearson's chi-squared

Table 3

AAT use before hospitalization

	Without AAT (n=33)	1 AAA (n=252)	2 AAAs (n=160)	3 AAAs (n=22)	4 AAAs (n=4)
Free from relapse	12 (36,4%)	113 (44,8%)*	56 (35,0%)	8 (36,4%)	1 (25,0%)
CAD	2 (6,1%)	53 (21,0%)*	65 (40,6%)	9 (40,9%)	2 (50,0%)
HF	14 (42,4%)	82 (32,5%)*	70 (43,8%)	13 (59,1%)	1 (25,0%)
HTN	9 (27,3%)	105 (41,7%)*	46 (28,8%)	6 (27,3%)	2 (50,0%)
Ic	-	54 (21,4%)*	68 (42,5%)	10 (45,5%)*	4 (100,0%)
• Propaphenone	-	42 (16,7%)*	44 (27,5%)	7 (31,8%)*	4 (100,0%)
• Allapinin® [Lappaconitine hydrobromide]	-	12 (4,8%)*	24 (15,0%)	3 (13,6%)	2 (50,0%)
III	-	115 (45,6%)*	112 (70%)*	22 (100,0%)	4 (100,0%)
• Amiodarone	-	57 (22,6%)*	82 (50,0%)	15 (68,2%)	2 (50,0%)
• Sotalol	-	58 (23,0%)	30 (18,8%)	7 (31,8%)	2 (50,0%)
beta-blockers	-	76 (30,2%)*	119 (74,4%)	19 (86,4%)	4 (100,0%)
CCB	-	7 (2,8%)*	21 (13,1%)	14 (63,6%)	4 (100,0%)

Note: * — P<0,05.

Abbreviations: AAA — antiarrhythmic agent, CAD — coronary artery disease, HF — heart failure, HTN — hypertension, CCB — calcium channel blockers.

Table 4

AAT and comorbidity

	CAD (n=132)	HTN (n=167)	HF (NYHA ⩾2) (n=184)	Comorbidity free (n=30)
Ic	51 (38,6%)	74 (44,3%)	79 (42,9%)	16 (53,3%)
III	110 (83,3%)*	124 (74,3%)	144 (78,3%)	20 (66,7%)
beta-blockers	93 (70,5%)	108 (64,7%)	137 (74,5%)*	19 (63,3%)
CCB	32 (24,2%)	30 (18,0%)	37 (20,1%)	5 (16,7%)

Note: * — P<0,05.

Abbreviations: CAD — coronary artery disease, HF — heart failure, HTN — hypertension, CCB — calcium channel blockers, NYHA — New York Heart Association.

test was used. Analysis of AAT administration predictors was carried out using multinomial logistic regression. The differences were considered significant at P<0,05.

Results

Clinical characteristics of patients. The study included 476 people of the Russian population (men — 57,1%; mean age — 57,1±8,7 years). Paroxysmal AF was the most common — 67,2%, persistent AF — 19,7%, long-standing persistent AF — 11,1%; in 9 patients (1,9%), the type of AF was not verified. A visit 12 months after ablation was performed in 392 (84,4%) patients. Among patients, there were following comorbidities: HTN — 167 (35,1%); NYHA class ⩾II heart failure (HF) — 184 (38,7%), of which 6 patients had reduced left ventricular ejection fraction (LVEF<50%); coronary artery disease (CAD) — 132 (27,7%).

Postoperative complications were recorded in 22 (4,6%) patients and most often (n=13) were associated with approach to the femoral vessels (hematomas and pseudoaneurysms).

Antiarrhythmic therapy. Before hospitalization, the majority of patients (n=439; 92,2%) received AAT. In the future, there was a peak AAT use in the 3-month period after the AF ablation (n=463; 97,3%) and a further slight decrease to 370 (94,8%) in the 6-month period and to 307 (78,7%) by the 12-month visit. Moreover, 27 (6,9%) patients received class IC AAT, 130 (33,3%) — class III, 180 (46,2%) — beta-blockers, and 36 (9,2%) — CCB. The frequency of using various AAT during the follow-up period is presented in Table 2.

AF recurrence. Early AF recurrence (within the first 3 months after ablation) was recorded in 102 (30,8%) patients. Within the remaining follow-up period, arrhythmia recurrence was reported in 125

(32,1%) patients. The administration of propafenone in the postoperative period was associated with the course without early recurrence (Po=0,17, P=0,04).

In patients who continued AAT, AF recurrence was recorded in 203 (52,1%) cases. At the same time, the highest recurrence rate was observed in patients with an initially paroxysmal AF — 69,5%, persistent AF — 19,2%, and long-standing persistent AF — 11,3% (P<0,01).

There were no significant associations of AF recurrence with specific antiarrhythmic agents.

Out of 307 (78,7%) patients who continued the prescribed AAT, 187 (47,9%) did not have AF recurrence during the entire follow-up period. Of these, 5 (2,7%) patients continued to take class IC agents, 35 (18,7%) patients — class III (7 — Amiodarone and 28 — Sotalol). In addition, 92 (49,2%) patients continued to take beta-blockers and 18 (9,6%) patients — CCB. However, indications for using these drugs were not described in the database. At the same time, all 187 patients had comorbidities (75,4% — HTN; 41,7% — NYHA class ⩾2 HF; 31,6% — CAD). Univariate regression analysis did not reveal significant predictors of AAT continuation in patients without AF recurrence among the following clinical parameters: gender, age, AF type, early and late recurrence of arrhythmias in the postoperative period, and comorbidities. In this regard, multivariate regression analysis was not performed.

AAT use before hospitalization. Before hospitalization, patients took a different number of antiarrhythmic agents (Table 3). The largest group consisted of patients taking one antiarrhythmic agent (n=252). These patients had the highest rate of freedom from arrhythmia recurrence by a 12-month period: 44,8% vs 35,0%, P=0,049 (group of one and two antiarrhythmic agents, respectively: 44,8% vs 36,4%, P>0,05 (group of one agent and without AAT, respectively); 36,4% vs 25,0% (group of three and four agents, respectively). A lower recurrence rate was found in the subgroup with one ineffective antiarrhythmic agent compared to the subgroup with a large number of drugs used (RR=0,85; 95% CI 0,73-0,98; P=0,03).

AAT and comorbidity. As expected, AAT differed depending on comorbidities of patients (Table 4). Thus, a group of patients with CAD received the largest number of class III agents and CCB before and during hospitalization (P<0,01). Patients with HF had the highest rate of taking beta-blockers. Patients without structural heart disease used class IC agents more often (P<0,05).

HTN correlated with a rarer use of Allapinin at all follow-up stages (Po=-0,150; P<0,05).

Discussion

Several important results were obtained. The use of AAT decreases 3 months after AF ablation, which corresponds with current recommendations. Nevertheless, there remains a category of patients with continuing AAT up to 12 months or more without documented AF recurrence. It is important that our study did not reveal clinical factors associated with prolonged AAT without indications.

A large proportion of patients continued AAT in the postoperative period, which may be due to their subjective signs even without documented arrhythmia recurrence on ECG. It can be assumed that the true recurrence rate could be underestimated, and continued therapy is associated with complaints. On the other hand, as shown in previous results, in some patients post-operative arrhythmias were detected using implantable cardiac monitors, which is associated with more reliable identification of asymptomatic and short-term arrhythmias [8]. Nevertheless, the fact of the common AAT use, including in patients without documented arrhythmia recurrence, requires attention and informing specialists caring for patients after ablation.

The lowest recurrence rate was found in patients with a minimal number of AAT in history (1 agent), which indicates the likely need for an earlier decision to conduct ablation, rather than continuing to select AAT after the first failure. This conclusion is consistent with official indications for AF ablation [1, 2].

During the first three months after ablation, there was a peak in the use of class IC agents with a subsequent decrease in their prescription. This indicates the preferred use of these drugs for prophylaxis in the first months of the postoperative period in patients without structural heart disease.

Over the past 15-20 years, the narrative of AAT in AF has changed, which reflects clinical guidelines for the management of AF [6, 10, 11]. To date, conservative therapy remains first-line approach. However, the use of AAT in patients after AF ablation is less standardized. AAT is associated with a risk of complications, therefore, their use should be considered individually, and the need to continue or withdrawal should be made every time when consulting patients. For example, in case of early arrhythmia recurrence (first 3 months after ablation), AAT is justified. In approximately 40% of cases, such arrhythmia recurrences are not recorded in long-term period, and AAT can be canceled [12]. Thus, assessing the need for therapy at each visit and informing patients can help reduce the frequency of use of unnecessary therapy and reduce the risk of its complications.

Clinical trials comparing AF ablation and AAT showed that AAT use in the 3-month postablative period significantly reduces the risk of early recur-

rence. However, long-term administration of AAT did not show a significant advantage in rhythm control [3, 13, 14].

The POWDER-AF study compared the efficacy of long- (1 year) and short-term (3 months) AAT. The study showed a lower incidence of symptomatic arrhythmia recurrence (2,7% vs 21,9%, P<0,001) and reablation (1,4% vs 19,2%, P<0,01) in the long-term AAT group; quality of life did not differ between groups. However, there were few patients with organic heart disease (9%), which does not reflect actual clinical practice [8]. Further clinical studies are needed for a comprehensive analysis of this.

Study limitations. Limitations include the voluntary participation of specialists in the study, non-standardized AAT protocols, and intermediate patient observations. The main limitations of the Register were published earlier [9, 15].

Conclusion

The frequency of AAT after AF ablation is significantly reduced. However, there is a cohort of patients without documented arrhythmia recurrence still receiving AAT. There were no clinical predictors of continued AAT in subjects without arrhythmia recurrence. Clinicians need to be better informed of approaches to AAT after AF.

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Appendix 1. Executive Committee and Register Researchers

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