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Early initiation of anti-relapse antiarrhythmic therapy in patients with atrial fibrillation and flutter after pharmacological cardioversion with refralon

Aim	Evaluating the efficacy and safety of early administration of antirecurrence antiarrhythmic therapy (AAT) following restoration of sinus rhythm (SR) with refralon.
Material and methods	The study included 247 patients with atrial fibrillation/atrial flutter (AF/AFL) (142 men) who underwent pharmacological cardioversion (PCV) with refralon. A 4-step schedule of drug administration was used (successive intravenous infusions at doses of 5, 5, 10, and 10 μg/kg; maximum total dose was 30 μg/kg). Patients who recovered SR and had no contraindications were prescribed antirecurrence AAT in the early (≤24 h; n=101) or delayed (≥24 h; n=95) period. Lappaconitine hydrobromide, propafenone, and sotalol were administered orally as the antirecurrence therapy. The decision on the time of initiating ATT and the choice of the drug and its dose was taken by the attending physician individually. The safety criteria included a prolonged PQ interval >200 ms; second- or third-degree atrioventricular block; QRS complex duration >120 ms; QT prolongation >500 ms; and heartbeat pauses >3 s. The efficacy criteria included the absence of sustained recurrence of AF/AFL after initiation of AAT and the duration of hospitalization after PCV. Patients were followed up during the study until they were discharged from the hospital.
Results	SR was recovered in 229 (92.7%) patients. In the group of early AAT initiation, a PQ duration >200 ms was observed in 8 (7.9%) patients, whereas in the group of delayed AAT initiation, in 7 patients (7.4%; p=1.000). A wide QRS complex >120 ms was recorded in 1 (1.1%) patient of the delayed AAT initiation group and in none of the patients of the early AAT initiation group (p=0.485). Ventricular arrhythmogenic effects and QT prolongation >500 ms were not detected in any patient. Numbers of early AF recurrence did not differ in the groups of early and delayed AAT initiation: 6 (5.9%) vs. 5 (5.3%), respectively (p=1.000). Median duration of hospitalization after PCV was 4 days in the group of early AAT initiation and 5 days in the group of delayed AAT initiation (p=0.009).
Conclusion	Early initiation of the refralon AAT does not increase the risk of drug adverse effects and reduces the duration of stay in the hospital.

Keywords	Atrial fibrillation; atrial flutter; cardioversion; antiarrhythmic drug; rhythm and conduction disorders
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Introduction

Atrial fibrillation (AF) is one of the most prevalent forms of arrhythmia in clinical practice affecting more than 33 million people worldwide. This type of arrhythmia develops in more than 5 million people annually. The incidence of AF is projected to double over the next 20 years [1].

AF is associated with the risk of developing life-threatening conditions due to high and irregular heart rate (HR), which can lead to hemodynamic disorders, heart failure (HF), and an increased risk of cardioembolic complications. All the above increases the risk of death [2–4].

HR control and rhythm control are two main strategies for managing patients with this form of arrhythmia. It was long thought that both strategies were equal in terms of disease prognosis and the effect on all-cause mortality. However, the results of the recent EAST-AFNET 4 study, which included elderly patients with a short history of AF, showed that early rhythm control was more effective

in reducing the likelihood of reaching the composite endpoint of that study (cardiovascular death, ischemic stroke, acute coronary syndrome, hospitalization for decompensated HF) [5].

Both electrical and drug-induced cardioversion can be used to restore the sinus rhythm (SR). Refralon – the Russian class III antiarrhythmic drug (AAD) – is the only drug with documented efficacy comparable with electrical cardioversion in patients with AF and atrial flutter (AFL). Refralon 10–30 μg/kg allows achieving SR restoration in 91.6% of patients with AF/AFL. This drug is also highly safe [6, 7].

Any method of cardioversion is associated with recurrent AF/AFL. The incidence of such recurrences ranges from 71% to 84% [8]. Preventive antiarrhythmic therapy (AAT) plays an important role in maintenance of SR. Early administration of AAT after successful cardioversion was shown to reduce the number of arrhythmia recurrences [9]. At the same time, AAT after the restoration of SR using Refralon may be associated with a potential risk of dangerous manifestations of drug interactions – proarrhythmic effects most particularly. The best timing of the antirecurrence AAT is unknown for such patients. All the above served as the basis for this study.

Objective

Evaluate the efficacy and safety of early antirecurrence AAT after restoration of SR using Refralon.

Material and methods

The study included 247 (142 male and 105 female) patients with AF/AFL who were subjected to an attempt of Refralon-induced cardioversion in the National Cardiology Research Center (Russian Federation) from 2018 to 2021. AF and AFL were detected in 209 and 38 patients, respectively. Persistent AF/AFL was observed in 161 patients. The median duration of a stopped episode of arrhythmia was 2160 [720; 4320] hours. Paroxysmal AF/AFL was confirmed in 86 patients. The median duration of a stopped episode of arrhythmia was 48 [24; 120] hours in those patients. The most prevalent concomitant cardiovascular diseases were hypertensive heart disease (81%), chronic HF (15%), and coronary artery disease (CAD) (11.8%). General clinical characteristics of subjects are presented in Table 1.

The restoration of SR with Refralon was carried out after a preliminary examination, which included total blood count and biochemical blood test, determination of thyroid hormones, electrocardiogram (ECG), and transthoracic echocardiography. Transesophageal echocardiography was performed to exclude intracardiac thrombosis in patients with AF/AFL lasting more than 48 hours. Moreover, all patients received anticoagulant therapy in accordance with the guidelines for preparation for cardioversion [10, 11].

Table 1. General clinical characteristics of patients (n=247)

Parameter	Value
Ratio of persistent and paroxysmal forms of AF/AFL, n	161/86
AF/AFL ratio, n	209/38
Sex (male/female), n	142/105
Age, years	64 [57; 70]
Body mass index, kg/m2	30 [27; 35]
Duration of a stopped episode of persistent AF/AFL, h	2160 [720; 4320]
Duration of a stopped episode of paroxysmal AF/AFL, h	48 [24; 120]
Hypertensive heart disease, n (%)	200 (81)
Coronary artery disease, n (%)	28 (11.8)
Postinfarction cardiosclerosis, n (%)	12 (4.9)
History of angioplasty with stenting, n (%)	18 (7.2)
Chronic heart failure, n (%)	37 (15)
NYHA class I/II, n	9/28
Hypertrophic cardiomyopathy, n (%)	2 (0.8)
History of cerebrovascular accident, n (%)	14 (5.7)
Diabetes mellitus, n (%)	30 (12.1)
Chronic obstructive pulmonary disease, n (%)	9 (3.6)
Bronchial asthma, n (%)	2 (0.8)
Obstructive sleep apnea, n (%)	11 (4.5)
CHA_2DS_2 VASc score	2 [1; 3]

The tabulated data is presented as the medians and interquartile ranges (Me [25th percentile; 75th percentile] if not otherwise specified. AF/AFL, atrial fibrillation/atrialflutter.

Refralon was administered in the intensive care unit under continuous ECG monitoring for up to 24 hours after dosing.

Drug-induced cardioversion consisted of 4 consecutive stages. Intravenous administration of a 0.1% solution of Refralon 5 μg/kg of body weight diluted in 20 mL of isotonic sodium chloride solution, for 2–3 minutes.

If there is no effect (SR not restored), intravenous administration of 0.1% Refralon solution at a dose of 5 μg/kg of body weight (total dose 10 μg/kg of body weight) was repeated in 15 minutes.

If there was no effect (SR not restored), another intravenous administration of 0.1% Refralon solution at a dose of 10 μg/kg of body weight (total dose 20 μg/kg of body weight) was performed in 15 minutes.

If there was no effect (SR not restored), the last intravenous administration of 0.1% Refralon solution at

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a dose of 10 μg/kg of body weight was performed in 15 minutes. Thus, the maximum total dose of Refralon was 30 μg/kg of body weight.

The drug was discontinued at any stage in the case of: SR restoration; a decrease in the ventricular contraction rate <50 bpm; an increase in the duration of QT interval >500 msec; the onset of proarrhythmic effects; any changes in the patient's condition that required additional medical interventions.

Patients with restored SR after the administration of Refralon who had no contraindications received antirecurrence AAT in the early (up to 24 hours) or delayed (more than 24 hours) period. The following drugs were administered orally as maintenance AAT: lappaconitine hydrobromide 50–75 mg/day, propafenone 450 mg/day, sotalol 120–160 mg/day. The decision on the time of starting AAT, the choice of the drug and its dose was made by the attending physician individually based on the patient's clinical condition, concomitant cardiovascular and extracardiac disorders, history of AAT, blood pressure (BP), ECG parameters (HR, duration of PQ, QRS, QT intervals).

The efficacy and safety of AAT were assessed using daily ECG and Holter monitoring on the day of cardioversion and on day 3 of AAT.

ECG abnormalities requiring discontinuation or reduction of the drug dose were used as safety criteria of the administered AAT:

- Atrioventricular (AV) block grade I (PQ >200 msec);
- AV block grade II–III; QRS prolongation >120 msec;
- QT prolongation >500 msec; cardiac pauses >3 s;
- The need to cancel or reduce the drug dose for other reasons.

Efficacy criteria for the administered AAT:

- absence of persistent recurrences of AF/AFL (more than 30 s) after the start of AAT;
- duration of hospital stay after cardioversion.

Patients were followed up during the study until they were discharged from the hospital.

The study was performed following the Good Clinical Practice. The study was approved by the ethics committee of the Russian National Cardiology Research Center.

Statistical analysis of the data obtained was carried out in StatTech v. 2.8.5 (OOO Stattech, Russian Federation). Quantitative indicators were assessed for normal distribution using the Shapiro–Wilk test (if less than 50 subjects) or the Kolmogorov–Smirnov test (if more than 50 subjects). Normally distributed quantitative indicators were described using the arithmetic means and standard deviations (M±SD). Non-normally distributed quantitative variables were described using the medians and interquartile ranges (Me [25th percentile; 75th percentile]). Categorical data were expressed by the absolute values and percentages. Two groups were compared by normally distributed quantitative indicators using the Student's t-test. Two groups were compared by non-normally distributed quantitative indicators using the Mann–Whitney U-test. Percentages were compared in the analysis of four-fold conjugation tables using the Pearson chi-square test and Fisher's exact test if the expected event was less than 10. The differences were statistically significant with $p < 0.05$.

Results

Drug-induced cardioversion using a 4 stage Refralon regimen was effective in 229 of 247 patients (total efficacy of the drug 92.7%; Figure 1). SR was registered within 15 minutes after dosing 5 μg/kg in 89 (36%) patients. SR was restored in 59 (59.9%) patients after the second dose of Refralon 5 μg/kg. SR was restored after the administration of a total dose of 20 μg/kg in 46 (78.5%) patients. Arrhythmia was resolved in another 35 (92.7%) patients after a total dose of 30 μg/kg.

Antirecurrence AAT was not administered 33 of the 229 patients with restored SR after the administration of Refralon for various reasons: 10 patients had a first-onset AF, which made it possible to refrain from AAT; another 4 patients had contraindications to the administration of AAP; 3 patients after successful restoration of SR had an early recurrence of AF, for which rate-reducing therapy was ordered; another 16 patients started treatment with beta-blockers.

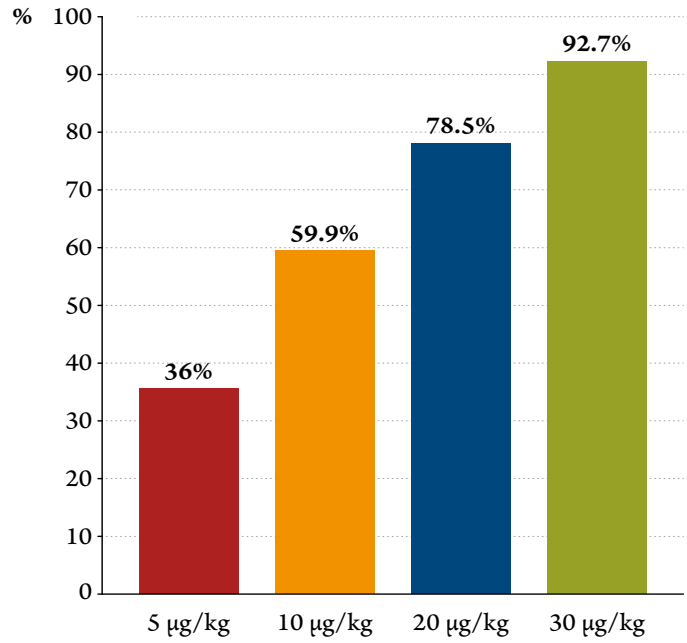
Preventive AAT was administered in all other cases of successful restoration of SR (n=196). It was ordered by the attending physicians within 24 hours from drug-induced cardioversion in 101 patients (early AAT group). AAT was started 24 hours after drug-induced cardioversion in 95 patients (delayed AAT group).

The clinical characteristics of the early and delayed AAT groups and the dose of Refralon used for drug-induced cardioversion are presented in Table 2.

The early and delayed AAT groups did not differ in the Refralon doses administered, demographics, and most clinical examination findings. However, there were significantly more patients with CAD and a history of transluminal coronary angioplasty (TCA) in the delayed AAT group. CHA_2DS_2 VASc scores were also higher in this group.

IC-class drugs (lappaconitine hydrobromide, propafenone) that do not affect the QT duration were administered more often in patients in the early AAT group (Table 3). That choice was made to reduce the risk of ventricular arrhythmogenic effects of drug interactions with Refralon. This strategy of antirecurrence therapy

Figure 1. Accumulated efficacy of Refralon in patients with AF/AFL depending on dose



AF, atrial fibrillation; AFL, atrial flutter.

led to the predominance of patients with a history of concomitant CAD and TCA in the delayed AAT group, since those patients had contraindications to Ic-class AAP, and sotalol, which prolongs the QT interval, was administered more often.

No life-threatening complications were reported in any of the study groups during AAT. No significant differences were found between the groups in any ECG parameters selected as the safety criteria for AAT (Table 4).

AV block grade I (PQ >200 msec) was detected only during the use of IC-class drugs (lappaconitine hydrobromide, propafenone). The PQ interval prolongation >200 msec was observed in 8 patients in the early AAT group and 7 patients in the delayed AAT group. The differences were statistically insignificant. The maximum duration of the PQ interval was 300 msec and was observed in the delayed AAT group during the administration of lappaconitine hydrobromide 75 mg/day. This patient also had QRS complex prolongation to 130 msec, which required reducing the dose to 50 mg/day. No QRS prolongation >120 msec was noted in the early AAT group.

AV block grade II or III did not develop during the early or delayed administration of AAT. Pathological QT prolongation >500 msec after the initiation of AAP was also not observed in any of the study groups.

Cardiac pauses >3 s were registered in 1 of 95 patients in the delayed AAT group. The maximum duration of cardiac pause was 4.8 sec without clinical manifestations. Those pauses occurred during the administration of lappaconitine hydrobromide 50mg/day due to sinoatrial block grade II–III. The drug was discontinued. Cardiac pauses were not observed in the early AAT group.

Table 2. Clinical characteristics of patients in early and delayed AAT groups

Parameter	Early AAT group (n=101)	Delayed AAT group (n=95)	p
Age, years	62.3±10.2	65.0±12.3	0.081
Sex (male/female), n	57 / 44	52 / 43	0.811
Paroxysmal AF n (%)	37 (36.6)	26 (27.4)	0.165
Persistent AF, n (%)	64 (63.4)	69 (72.6)	
Effective dose of Refralon, n (%)			
• 5 μg/kg	44 (43.6)	33 (34.7)	0.206
• 10 μg/kg	22 (21.8)	25 (26.3)	0.458
• 20 μg/kg	23 (22.8)	16 (16.8)	0.299
• 30 μg/kg	12 (11.9)	21 (22.1)	0.056
HHD, n (%)	83 (82.2)	79 (83.2)	0.856
CAD, n (%)	3 (3.0)	16 (16.8)	0.001
History of TCA, n (%)	0	8 (8.4)	0.003
PICS, n (%)	1 (1.0)	6 (6.3)	0.059
CHF, n (%)	11 (10.9)	19 (20.0)	0.077
CHF NYHA class II	1 / 10	0 / 19	0.125
HCM, n (%)	0	1 (1.1)	0.485
History of CVA, % (n)	7 (6.9)	6 (6.3)	1.000
DM, n (%)	13 (12.9)	11 (11.6)	0.783
COPD, n (%)	6 (5.9)	3 (3.2)	0.499
BA, n (%)	1 (1.0)	1 (1.1)	1.000
OSA, n (%)	4 (4.0)	6 (6.3)	0.528
CHA_2DS_2 VASc score	2	3	0.015

AAT, antiarrhythmic therapy; TCA, transluminal coronary angioplasty; PICS, postinfarction cardiosclerosis; HCM, hypertrophic cardiomyopathy; CVA, cerebrovascular accident; BA, bronchial asthma; OSA, obstructive sleep apnea.

The drug was discontinued, or the dose was reduced in 2 patients for other reasons. One patient in the early AAT group had an increase in BP to 170/90 mm Hg during the administration of lappaconitine hydrobromide 75 mg/day, and therefore the dose was reduced to 50 mg/day.

Pacing threshold increased in one patient in the delayed AAT group during the administration of lappaconitine hydrobromide 75 mg/day. Pacing threshold returned to the baseline level after the drug was discontinued.

Indicators of the efficacy of early and delayed AAT administration are presented in Table 5. There were no significant differences in the selected efficacy criteria except for the duration of hospital stay after Refralon-induced cardioversion.

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After the restoration of SR during hospital stay, stable (more than 30 s) recurrences of AF/AFL were noted in 11 (5.2%) of 212 patients – 6 (5.9%) in the early AAT group and 5 (5.3%) in the delayed AAT group.

The time to recurrence after successful drug-induced cardioversion in the early AAT group was 14 [4; 20] hours. The mean duration of a new-onset episode of arrhythmia was 10±11 hours. SR restored spontaneously in 4 of 6 patients with recurrent AF/AFL in this group. One patient underwent electrical cardioversion on day 2 after the recurrence of arrhythmia. No further attempts were made to correct arrhythmia in another patient.

The time to recurrence after successful drug-induced cardioversion in the delayed AAT group was 2 [2; 12] hours with the mean duration of the recurrence episode of 8±4 hours. SR restored spontaneously in 3 patients of this group. Repeated Refralon-induced cardioversion was conducted in another 2 patients, after which persistent SR was recorded during AAT through the follow-up period.

It is shown in Table 5 that hospital stay after successful drug-induced cardioversion was longer in the delayed AAT group.

Discussion

The study was first to show the safety of early administration of maintenance AAT after drug-induced cardioversion in patients with paroxysmal and persistent AF/AFL (maintenance AAT had been administered not earlier than 24 hours after drug-induced cardioversion). In the early AAT group, there was no prevalence of adverse effects chosen as the safety criteria of the treatment (see Table 3), compared to the delayed AAT group. Most of the adverse effects of maintenance AAT were not clinically significant and did not cause treatment discontinuation in either patient group.

AF recurrences after successful Refralon-induced cardioversion were rare (11 (5.2%) patients). Most recurrences resolved spontaneously. Only 3 patients required repeated cardioversion. It should be noted that neither the total number of AF recurrences nor the number of AF recurrences that required repeated cardioversion were significantly different between the early and delayed AAT groups. Early recurrences of AF after drug-induced cardioversion may be due to electrical remodeling of the atrial myocardium caused by long-term arrhythmia (among patients included in the study, those with persistent AF predominated, the total duration of AF was more than 12 months in most patients with recurrent arrhythmias) [12]. A history of failure of one or more AAPs to prevent AF recurrence in several patients is also indirect evidence of electrical remodeling of the atrial myocardium.

Table 3. Antiarrhythmic drugs administered in early and delayed AAT groups

Drug	Early AAT group (n=101)	Delayed AAT group (n=95)	p
Lappaconitine hydrobromide 50–75 mg/day, n (%)	79 (78.2)	50 (52.6)	0.714
Propafenone 450 mg/day, n (%)	16 (15.8)	6 (6.3)	0.151
Sotalol 120–160 mg/day, n (%)	17 (16.8)	55 (57.8)	0.023

AAT, antiarrhythmic therapy.

Table 4. ECG abnormalities as the safety criteria of early and delayed AAT

Criterion	Early AAT group (n=101)	Delayed AAT group (n=95)	p
AV block grade I (PQ >200 msec), n (%)	8 (7.9)	7 (7.4)	1.000
AV blockade grade II–III	0	0	–
QRS prolongation >120 msec, n (%)	0	1 (1.1)	0.485
QT prolongation >500 msec	0	0	–
Cardiac pauses >3 sec, n (%)	0	1 (1.1)	0.485
The need to cancel or reduce the drug dose for other reasons, n (%)	1 (1.0)	1 (1.1)	1.000

AAT, antiarrhythmic therapy, AV, atrioventricular.

Table 5. Indicators of the efficacy of early and delayed AAT

Parameter	Early AAT group (n=101)	Delayed AAT group (n=95)	p
Recurrence of AF after initiation of AAT, n (%)	6 (5.9)	5 (5.3)	1.000
Time of recurrence after DIC, h	14 [4; 20]	2 [2; 12]	0.449
Duration of recurrence, h (M±SD)	10.2±2.9	8.1±4.3	0.640
Cardioversion of AF recurrence, n (%)	1 (0.9)	2 (1.9)	0.606
Rate-reducing therapy for AF recurrence, n (%)	1 (0.9)	0	1.000
Time in hospital after DIC, days	4 [3; 6]	5 [4; 6]	0.009

AAT, antiarrhythmic therapy, DIC, drug-induced cardioversion.

Despite the absence of significant differences in the number of AF recurrences in both study groups, early AAT after Refralon-induced cardioversion significantly reduced the duration of hospital stay by 1 day (p=0.009). The 24 hour interval after drug-induced cardioversion, during which patients were monitored without using AAT, caused longer hospital treatment in delayed AAT.

The retrospective design and lack of randomization are significant мrlimitations of the study. The decision on the early or delayed maintenance AAT after Refralon-induced cardioversion was made and the drug was chosen by the attending physician given the clinical picture of the disease, previous experience of AAT, the nature of the drug effect on the myocardial depolarization and repolarization processes, and the corresponding ECG parameters. A natural consequence was the predominance of AAP class IC in the early AAT group, since their mechanism of action is different from that of Refralon, they do not affect the QT interval duration, and their early administration in the case of potential interaction with Refralon is associated with a lower risk of ventricular arrhythmogenic effect due to the pathological QT interval prolongation. Class III drug sotalol with similar pharmacodynamic effects, primarily the effect on the QT interval duration, was administered in a significantly fewer patients in the first 24 hours after drug-induced cardioversion.

It should also be noted that fewer patients in the early AAT group had concomitant CAD, a history of TCA (5.4% versus 16.8% and 0 versus 7.9%; p=0.008 and p=0.002, respectively), which was less restrictive of the use of IC-class drugs in patients in this group, for whom any manifestation of CAD is a contraindication. All the above requires a specially designed study to assess the safety of early administration of AAT after drug-induced cardioversion using Refralon in patients with CAD.

Conclusions

1. The administration of antiarrhythmic therapy early after Refralon-induced cardioversion is safe and allows reducing the duration of hospital stay.
2. Recurrences of atrial fibrillation after successful Refralon-induced cardioversion are rare, their rates do not differ significantly between the groups of early and delayed administration of antiarrhythmic drugs.

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No conflict of interest is reported.

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REFERENCES

1. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of Current and Future Incidence and Prevalence of Atrial Fibrillation in the U.S. Adult Population. The American Journal of Cardiology. 2013;112(8):1142–7. DOI: 10.1016/j.amjcard.2013.05.063
2. Osmolovskaya Yu.F., Romanova N.V., Zhirov I.V., Tereschenko S.N. Epidemiology and management of heart failure patients with atrial fibrillation. Medical Council. 2016;10:93–7. [Russian: Осмоловская Ю.Ф., Романова Н.В., Жиров И.В., Терещенко С.Н. Эпидемиология и особенности терапии хронической сердечной недостаточности в сочетании с фибрилляцией предсердий. Медицинский Совет. 2016;10:93-7]. DOI: 10.21518/2079-701X-2016-10-93-97
3. Agarwal M, Apostolakis S, Lane DA, Lip GYH. The Impact of Heart Failure and Left Ventricular Dysfunction in Predicting Stroke, Thromboembolism, and Mortality in Atrial Fibrillation Patients: A Systematic Review. Clinical Therapeutics. 2014;36(9):1135–44. DOI: 10.1016/j.clinthera.2014.07.015
4. Shkolnikova MA, Jdanov DA, Ildarova RA, Shcherbakova NV, Polyakova EB, Mikhaylov EN et al. Atrial fibrillation among Russian men and women aged 55 years and older: prevalence, mortality, and associations with biomarkers in a population-based study. Journal of geriatric cardiology. 2020;17(2):74–84. DOI: 10.11909/j.issn.1671-5411.2020.02.002
5. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. New England Journal of Medicine. 2020;383(14):1305–16. DOI: 10.1056/NEJMoa2019422
6. Mironov N.Yu., Yuricheva Yu.A., Vlodzyanovskiy V.V., Sokolov S.F., Dzaurova Kh.M., Golitsyn S.P. et al. Safety and Effectiveness of Pharmacologic Conversion of Atrial Fibrillation and Flutter: Results of Multicenter Trial. Part I: Study Rationale, Design and Assessment of Effectiveness. Rational Pharmacotherapy in Cardiology. 2021;17(2):193–9. [Russian: Миронов Н.Ю., Юричева Ю.А., Влодзяновский В.В., Соколов С.Ф., Дзаурова Х.М., Голицын С.П. и др. Опыт клинического применения отечественного антиаритмического препарата III класса для медикаментозной кардиоверсии фибрилляции и трепетания предсердий: результаты многоцентрового исследования. Часть 1: методология исследования и оценка эффективности. Рациональная Фармакотерапия в Кардиологии. 2021;17(2):193-9]. DOI: 10.20996/1819-6446-2021-03-05
7. Kozlova L.K., Sokolova N.V., Sivkova A.V., Kamyshanova A.E., Abramova O.Yu., Kuchma G.B. et al. Experience of pharmacological cardioversion with refralon in persistent atrial fibrillation and flutter according to the data of the cardiology department of Orenburg regional clinical hospital. Journal of Arrhythmology. 2021;28(3):13–20. [Russian: Козлова Л.К., Соколова Н.В., Сивкова А.В., Камышанова А.Е., Абрамова О.Ю., Кучма Г.Б. и др. Опыт медикаментозной кардиоверсии рефралоном при персистирующей форме фибрилляции и трепетания предсердий по данным Оренбургской областной клинической больницы. Вестник аритмологии. 2021;28(3):13-20]. DOI: 10.35336/VA-2021-3-13-20
8. Schilling RJ. Cardioversion of atrial fibrillation: the use of antiarrhythmic drugs. Heart. 2010;96(5):333–8. DOI: 10.1136/hrt.2008.155812
9. Kirchhof P, Andresen D, Bosch R, Borggrefe M, Meinertz T, Parade U et al. Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation (Flec-SL): a prospec-

tive, randomised, open-label, blinded endpoint assessment trial. The Lancet. 2012;380(9838):238–46. DOI: 10.1016/S0140-6736(12)60570-4
10. Lucà F, Giubilato S, Di Fusco SA, Piccioni L, Rao CM, Iorio A et al. Anticoagulation in Atrial Fibrillation Cardioversion: What Is Crucial to Take into Account. Journal of Clinical Medicine. 2021;10(15):3212. DOI: 10.3390/jcm10153212
11. Shubik Yu.V., Medvedev M.M., Mikhaylov E.N., Gasimova N.Z., Gilyarov M.Yu. Management of atrial fibrillation in Russia: real clinical practice and current clinical guidelines. Journal of Arrhythmology. 2021;28(2):55–63. [Russian: Шубик Ю.В., Медведев М.М., Михайлов Е.Н., Гасымова Н.З., Гиляров М.Ю. Лечение фибрилляции предсердий в России: реальная клиническая практика и рекомендации. Вестник аритмологии. 2021;28(2):55-63]. DOI: 10.35336/VA-2021-2-55-63
12. Jalife J, Kaur K. Atrial remodeling, fibrosis, and atrial fibrillation. Trends in Cardiovascular Medicine. 2015;25(6):475–84. DOI: 10.1016/j.tcm.2014.12.015