https://doi.org/10.35336/VA-1289

RESULTS OF A PROSPECTIVE RANDOMIZED STUDY COMPARING EFFICACY AND SAFETY OF REFRALON AND AMIODARONE FOR CARDIOVERSION IN PATIENTS WITH PAROXYSMAL ATRIAL FIBRILLATION AND FLUTTER

D.A.Gagloeva[1], N.Yu.Mironov[1,2], Kh.M.Dzaurova[1], M.A.Zelberg[1], Yu.A.Yuricheva[1], S.F.Sokolov[1], S.P.Golitsyn[1]

[1]FSBI «NMRC Of Cardiology» named after academician E.I.Chazov of the MH RF, Russia, Moscow, 15a, 3rd-Cherepkovskaya str.; [2]FSBI of Higher Education «Plekhanov Russian University of Economics» Russia, Moscow, 36 Stremyannoy ln.

Aim. To compare efficacy and safety of refralon and amiodarone for cardioversion in patients with paroxysmal atrial fibrillation and flutter (AF/AFL).

Methods. The study included 60 patients (32 men and 28 women) with symptomatic paroxysmal AF/AFL. All patients underwent a preliminary examination to exclude contraindications to cardioversion. The procedure of pharmacological cardioversion was carried out in the intensive care unit. By the method of envelope randomization, patients were divided into equal groups of refralon and amiodarone, 30 participants each. Both groups did not differ significantly in terms of main clinical characteristics. Cardioversion with refralon consisted of four subsequent iv injections: 5-5-10-10 μg/kg of body weight at intervals of 15 minutes. Patients of the second group were intravenously administered amiodarone at a dose of 5 mg/kg of body weight for 20-60 minutes, depending on the tolerability of the drug. In case of AF/AFL maintaining after 60 minutes from the start of administration, the infusion of amiodarone 100 mg/h continued until restoration of sinus rhythm (SR) or until the maximal total dose of 1200 mg/day was reached. Patients were observed for 24 hours.

Results. SR restored in 96.7% (29 of 30) of patients in the refralon group, of which 56.7% (17 of 30) - after a dose of 5 μg / kg. In the amiodarone group SR restored in 53.3% (16 of 30) patients ($p<0.001$). Median time to arrhythmia conversion in refralon group was 14 [7;23] min, while in amiodarone group it was 150 [82;240] min ($p<0.001$). Within 60 minutes SR was restored in 26 patients in group of refralon and only in 4 patients in group of amiodarone ($p<0.001$). There were no statistically significant differences in the incidence of major adverse cardiac events, bradyarrhythmias, lowering of blood pressure, and QT prolongation between the groups.

Conclusion. In randomized trial Refralon demonstrated higher rate of successful AF/AFL conversion and shorter time to SR restoration than amiodarone. The most of patients restored SR after administration of the lowest dose of refralon, that ensures the safety of cardioversion.

Key words: atrial fibrillation; atrial flutter; refralon; amiodarone; pharmacological cardioversion; class III antiarrhythmic drugs

Conflict of interest: none.

Funding: The work was funded by governmental assignment №121031700336-7. The research was supported with grant №23-75-30012 from the Russian Science Foundation.

Received: 15.11.2023 **Revision received:** 27.11.2023 **Accepted:** 30.11.2023

Corresponding author: Diana Gagloeva, E-mail: gagloeva3005@gmail.com

D.A.Gagloeva - ORCID 0000-0002-9295-6813, N.Yu.Mironov - ORCID 0000-0002-6086-6784, Kh.M.Dzaurova - ORCID 0000-0003-4291-1040, M.A.Zelberg - ORCID 0000-0002-9295-6813, Yu.A.Yuricheva - ORCID 0000-0002-5532-6345, S.F.Sokolov - ORCID 0000-0001-5418-7796, S.P.Golitsyn - ORCID 0000-0001-9913-9974

For citation: Gagloeva DA, Mironov NYu, Dzaurova KhM, Zelberg MA, Yuricheva YuA, Sokolov SF, Golitsyn SP. Results of a prospective randomized study comparing efficacy and safety of refralon and amiodarone for cardioversion in patients with paroxysmal atrial fibrillation and flutter. *Journal of Arrhythmology.* 2024;31(1): 63-70. https://doi.org/10.35336/VA-1289.

Cardiac rhythm disorders are widespread clinical conditions and remain one of the most pressing problems of public health and modern cardiology. Among cardiac arrhythmias, atrial fibrillation (AF) and atrial flutter (AFt) are the most common. The detection rate of AF/AFt in the general adult population is about 2%. The incidence of AF/AFt is projected to increase due not only to increased life expectancy and aging of the population, but also to the increased prevalence of risk factors for the development of AF. Thus, according to the results of various population studies, the incidence of AF/AFt may increase 3-fold by 2050 [1-3].

According to the literature, the frequency of detection of paroxysmal form of AF/AFt ranges from 25% to 62%. However, the actual prevalence of this form of arrhythmia is significantly higher, because most epidemiologic studies assess only symptomatic AF/AFt, not taking into account asymptomatic forms of arrhythmia detected by long-term electrocardiogram (ECG) monitoring [4, 5].

There are two main strategies in the management of patients with AF/AFt, including heart rate control and rhythm control. Both electrical and drug-induced cardioversion (DIC) have been successfully used to restore sinus rhythm (SR) [1]. Pharmacologic cardioversion, in comparison with electrical cardioversion, allows not only to control arrhythmias, but also to prevent the development of early arrhythmia recurrences after successful restoration of SR. Also advantages of DIC are that the procedure is performed without sedation and there is no possible electrical trauma to the heart.

The choice of antiarrhythmic drug for the management of paroxysms of AF/AFt depends on a number of factors, including the existing cardiovascular and concomitant pathology, anamnestic information about previously used antiarrhythmic agents, and it is necessary to take into account the use of concomitant drug therapy. According to current clinical recommendations in the Russian Federation, IC (procainamide, propafenone) and class III (amiodarone, refralon) antiarrhythmic drugs are used to restore sinus rhythm.

Among the listed drugs, amiodarone is the most widely used. The effectiveness of the drug ranges from 30% to 90%. The highest rates of rhythm recovery are achieved by administering high doses (more than 1500 mg/day). However, in real clinical practice, amiodarone is most often used in the form of bolus (5-7 mg/kg body weight) and SR recovery is registered in 34-69% of cases. In addition, the use of amiodarone in clinical practice is often limited by pronounced undesirable effects and a wide range of interactions with other drugs [6, 7].

Since 2020, the National Clinical Recommendations «Atrial fibrillation and flutter in adults», approved by the Ministry of Health of Russia, include a domestic class III antiarrhythmic drug - Refralone [8]. The results of the conducted studies demonstrated high efficiency and safety of the drug use. During cardioversion with refralone (10 μg/kg to 30 μg/kg), recovery of SR was reported in more than 90% of patients with persistent AF/AFt [9].

It is important to note that restoration of SR using refralone in paroxysmal AF/AFt patients has been poorly studied. Higher SR recovery rates may be expected among patients with the paroxysmal course of these arrhythmias compared with the persistent form. It can also be expected that arrhythmia management will occur with the use of lower doses of the drug, which is likely to contribute to a lower incidence of adverse events. To justify a wider use of domestic antiarrhythmic drug in patients with paroxysmal AF/AFt, a comparative evaluation of the use of refralone and amiodarone for DIC in paroxysms of AF and AFt in a prospective randomized trial is important.

The aim of the study was to conduct a comparative evaluation of the efficacy and safety of DIC with refralone and amiodarone in patients with paroxysmal AF/AFt.

METHODS

The study included 60 patients (32 men and 28 women) with paroxysms of AF/AFt who had indications for restoration of sinus rhythm (SR) and who underwent an attempt of DIC with refralone or amiodarone on the basis of FGBU «Academician E.I.Chazov NMICC» of the Ministry of Health of Russia. The clinical characteristics of the study participants are presented in Table 1. As can be seen, the

Table 1.

Clinical and instrumental characteristics of the study participants

Indicator	All (n=60)	Refralone (n=30)	Amiodarone (n=30)	p
Age, years	65±11	63±13	67±8	0.151
Sex (male/female), years	32/28	15/15	17/13	0.605
Height, cm	173±10	173±11	173±8	0.979
Weight, kg	88 [78;100]	90 [80;100]	85 [75;100]	0.371
Body mass index, kg/m^2	29 [26;33]	30 [26;35]	28 [26;33]	0.574
Form of arrhythmia (AF/AFt), n	54/6	28/2	26/4	0.671
PD AF/AFt, h	36 [23;126]	60 [21;144]	24 [24;72]	0.135
PD AF/AFt > 24 h, n (%)	33 (55%)	19 (63.3%)	14 (46.7%)	0.194
PD AF/AFt < 24 h, n (%)	27 (45%)	11 (36.7 %)	16 (53.3%)	0.194
Hypertension, n (%)	54 (90.0%)	27 (90.0%)	27 (90.0%)	1.000
CHD, n (%)	11 (18.3%)	5 (16.7%)	6 (20.0%)	1.000
CAS history, n (%)	8 (13.3%)	4 (13.3%)	4 (14.3%)	1.000
Myocardial infarction history, n (%)	4 (6.7%)	2 (6.7%)	2 (6.7%)	1.000
CHD, n (%)	11 (18.3%)	5 (16.7%)	6 (20.0%)	1.000
NYHA FC I CHD, n (%)	4 (6.7%)	1 (3.3%)	3 (10%)	0.782
NYHA FC II CHD, n (%)	7 (11.7%)	4 (13.3%)	3 (10%)	
IS history, n (%)	4 (6.7%)	3 (10.0%)	1 (3.3%)	0.612
Diabetes mellitus, n (%)	8 (13.3%)	7 (23.3%)	1 (3.3%)	0.052
COPD, n (%)	7 (11.7%)	3 (10.0%)	4 (13.3%)	1.000
OSAS, n (%)	6 (10%)	4 (13.3%)	2 (6.7%)	0.671
Sum of CHA2DS2Vasc scores, n	3 [2;3]	3 [2;4]	2 [1;3]	0.121
LA volume, ml	77±21	79±18	75±24	0.484
LA anteroposterior dimension, cm	4±0	4±0	4±1	0.871
LV ejection fraction, %	60 [56;60]	60 [60;60]	60 [55;60]	0.114

Note: hereinafter data are presented as n - absolute number of observations, Me - median, [25;75] - 25th and 75th percentiles, M±SD - mean values and standard deviations; AF - atrial fibrillation; AFt - atrial flutter; PD - paroxysm duration; CHD - chronic heart disease; CAS - coronary artery stenting; CHF - chronic heart failure; FC - functional class; IS - ischemic stroke; COPD - chronic obstructive pulmonary disease; OSAS, obstructive sleep apnea syndrome; LA - left atrium; LV - left ventricle.

mean age of the patients included in the study was 65±11 years. In 54 patients, the arrhythmia was represented by AF (90.0%) and in 6 patients by AFt (10.0%). The duration of the managed arrhythmia episode was 36 [23;126] hours. The study included patients with concomitant cardiovascular diseases such as hypertension (90.0%), ischemic heart disease (18.3%), chronic heart failure (18.3%) (Table 1). At the time of inclusion in the study, the patients were not receiving drug antiarrhythmic therapy. The tactics of anticoagulant therapy was determined in accordance with the clinical recommendations of the Ministry of Health of the Russian Federation [7]. The structure of the study and the stages of its implementation are presented in Figure 1.

To identify the exclusion criteria, all patients underwent preliminary examination in the volume of: ECG registration, blood biochemical study, echocardiography, transesophageal echocardiography (in case of paroxysm duration more than 48 hours). Patients with paroxysms requiring immediate restoration of SR, bradysystolic arrhythmias, QT interval>440 ms, electrolyte disturbances and contraindications to cardioversion were not included in the study. In the absence of exclusion criteria, study participants were assigned to the refralone (n=30) and amiodarone (n=30) groups by envelope randomization. No significant differences in the presented characteristics (Table 1) among the formed groups were revealed.

DIC was performed in the intensive care unit (Fig. 1). Cardioversion with refralone was performed according to a four-stage drug administration scheme, according to which two injections at a dose of 5 μg/kg and two injections at a dose of 10 μg/kg were performed. The interval between injections was 15 minutes. The maximum total dose of the drug is 30 mcg/kg. DIC with amiodarone was performed in two stages. In the first stage, the drug was administered at a dose of 5 mg/kg for 20-60 minutes (as tolerated). If arrhythmia persisted after 60 minutes, the second stage was performed - prolonged infusion of amiodarone 100 mg/hour until recovery of SR or total dose of 1200 mg.

Drug administration was stopped in case of proarrhythmic effects, bradycardia <50 beats/min, increased QT interval duration>500 ms, and any changes urgently requiring additional medical manipulation. Follow-up of patients after DIC, as well as evaluation of efficacy (see Table 2) and safety (see Table 3) criteria, was performed for 24 hours. A detailed description of the study materials and methods (inclusion, non-inclusion and exclusion criteria, cardioversion protocols) is available at www.ClinicalTrials.gov (study identifier NCT05445297).

The study was carried out in accordance with the state standard «National Standard of the Russian Federation. Good Clinical Practice» and was approved by the independent ethical committee of the FGBU «Ak. E.I. Chazov» of the Ministry of Health of the Russian Federation. The detailed characterization of efficacy and safety criteria, the methods of statistical analysis and data processing used, and the preliminary results of the study have been published previously [10].

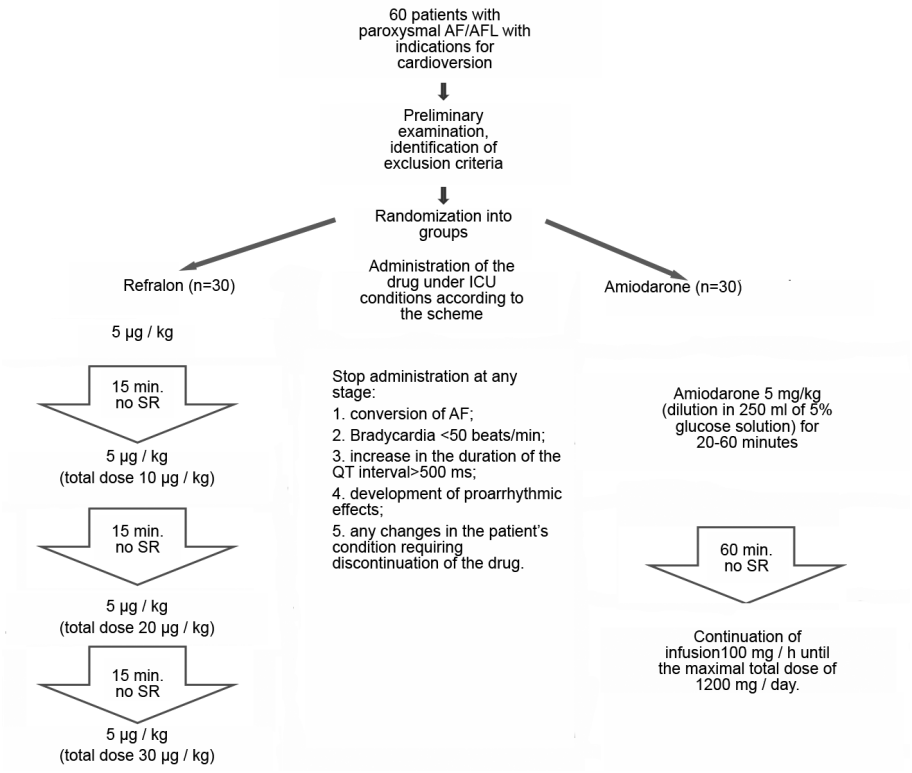

Fig. 1. Study design. Note: AF - atrial fibrillation, AFL - atrial flutter, SR - sinus rhythm, ICU - intensive care unit.

RESULTS

Performance evaluation

In DIC with refralone, recovery of SR within 24 h was recorded in 96.7% (29 of 30) patients, and in DIC with amiodarone, in 53.3% (16 of 30) patients; p<0.00 1 (Table 2). Administration of refralone at a dose of 5 mcg/kg relieved arrhythmias in 17 of 30 (56.7%) patients. After repeated adminis-

Table 2.

Indicators of the effectiveness of drug-induced cardioversion

Criterion	Refralon (n=30)	Amiodarone (n=30)	p
SRR during 24 hours, n (%)	29 (96.7%)	16 (53.3%)	< 0.001*
SRR during 60 minutes, n (%)	26 (86.7%)	4 (13.3%)	< 0.001*
Time to SRR, min	14 [7;23]	150 [82;240]	< 0.001**
Persistent arrhythmia recurrences[#], n	3/29	0/16	0.237

Note: SRR - sinus rhythm recovery; * - Fisher's exact test was used; ** - Mann-Whitney U-criterion was used; [#] - per number of SRR.

tration of the drug (total dose of 10 μg/kg), SR was registered in 24 patients (80%). Arrhythmia suppression after administration of refralone at a total dose of 20 mcg/kg was observed in 26 patients (86.7%). Administration of the maximum drug dose of 30 mcg/kg restored SR in 29 of 30 patients. Thus, the cumulative efficacy of Refralone was 96.7% (Figure 2). It should be noted that within 60 minutes from the start of refralone administration, 86.7% of patients (26 of 30) were able to recover SR (Figure 3).

In the DIC group with amiodarone within 60 minutes from the beginning of drug administration at a dose of 5 mg/kg, recovery of SR was registered in 4 out of 30 patients (13.3%) (Fig. 2-3). In the next phase of extended infusion of amiodarone, arrhythmia control occurred in 12 patients, bringing the cumulative efficacy of amiodarone to 53.3% (16 of 30 patients; Figure 2; Table 2). The rate of SR recovery with refralone is significantly superior to the rate of arrhythmia relief when amiodarone is administered. Differences in the time to achieve antiarrhythmic effect are more than tenfold. For example, in DIC with refralone, the median time to resolution was 14 [7;23] min, whereas in DIC with amiodarone, the median time to resolution was 150 [82;240] min (p<0.001; Table 2). AF recurrences were reported in 3 of 29 (10.3%) recovered SR patients in the refralone group. No recurrences were noted in the amiodarone group (p=0.237; Table 2).

Safety assessment

No acute cardiovascular complications, fatal outcomes were noted during the study. No paroxysmal ventricular rhythm disturbances were registered during the study (Table 3). An increase in QT interval duration of more than 500 ms was registered with equal probability in 6.7% (in two patients; p=1.00; see Table 3) in each of the studied groups. When refralone was used, the maximum values of QT interval (510 ms and 520 ms) were registered after the drug administration in doses of 20 μg/kg (immediately after SR recovery) and 30 μg/kg (against the background of persistence of AF, which was further eliminated after 3 hours), respectively.

In the amiodarone group, a significant increase in QT interval duration was observed in two patients during prolonged infusion of the drug. In the first patient, the maximum QT interval (520 ms) was recorded immediately after arrhythmia management. In the second patient the maximal QT value reached 570 ms against the background of persistence of AF after administration of the maximum daily dose of amiodarone (1200 mg). The QT interval duration in both cases normalized by the end of 24 hours of follow-up.

When analyzing the effect of refralone and amiodarone on the dynamics of QT and QTc intervals within a day after cardioversion, according to HM-ECG data, different patterns were revealed in the two treatment groups. When refralone is administered, QT/QTc prolongation relative to baseline values occurs predominantly in the first hours from the onset of DIC and tends to decrease gradually over 24 hours. In case of amiodarone administration, the picture is different: the duration of QT/QTc intervals relative to the initial points increases more slowly and reaches the maximum values by the middle of the 24-hour interval (Fig. 4).

In 1 patient (3.3%) after completion of the first stage of amiodarone infusion (total dose 400 mg) against the background of persisting AF, bradysystole developed, due to which the drug administration was discontinued. Bradysystole was not accompanied by clinical manifestations and resolved on its own. No bradyarrhythmias were recorded in the refralone group (p=1,000; Table 3).

Arterial hypotension with minimum BP values of 90/60 mmHg and 86/62 mmHg was noted in 2 patients (6.7%) after completion of the first stage of amiodarone infusion (administered 450 mg and 500 mg). Further administration of the drug was discontinued. There was no recovery of SR within 24 hours in these patients. No BP reduction was recorded in the refralone group (p=0.492; see Table 3).

The obtained results demonstrated a significant superiority of cardioversion efficacy of the domestic antiarrhythmic drug over amiodarone. More than half of the patients (56.7%) recovered SR after administration of a minimum dose of 5 mcg/kg refralon. Thus, the efficacy of

Table 3.

Indicators of safety of drug-induced cardioversion

Criterion	Refralon (n=30)	Amiodarone (n=30)	p
Paroxysmal ventricular arrhythmias, n	-	-	-
QT interval duration > 500 ms, n (%)	2 (6.7%)	2 (6.7%)	1.000
Bradycardia with HR <50 beats/min, n (%)	-	1 (3.3%)	1.000
Arterial hypotension, n (%)	-	2 (6.7%)	0.492

Note: HR - heart rate; p - Fisher's Exact Test.

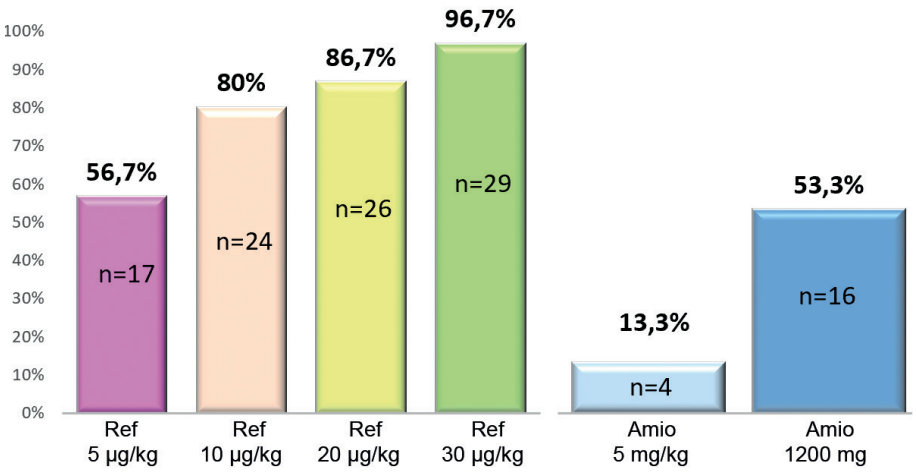

Fig. 2. Accumulated effectiveness of refralon (Ref) and amiodarone (Amio).

the lowest dose we studied, achieved within 15 minutes, was comparable to the maximum efficacy of amiodarone accumulated over 24 hours (53.3%; p=0.795) (Figure 2). The cumulative efficacy of refralone at doses up to 30 μg/kg accumulated over 24 hours was 96.7% (29 of 30) and significantly outperformed that of amiodarone at the maximum daily dose of up to 1200 mg (OR = 0.039; 95%; CI: 0.005 to 0.328; p<0.001). The superiority of refralone over amiodarone is also important in the speed of arrhythmia relief. Thus, SR was successfully restored within 60 min from the start of refralone administration in more than 80% of patients (Fig. 2-3).

It is known that in many cases paroxysms of AF and AFt are self-corrected. However, spontaneous relief is most likely within the first 24 h of paroxysm onset [11].

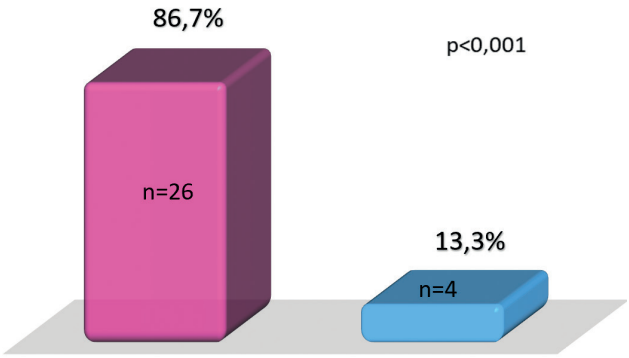

Fig. 3. Comparative efficacy of SR restoration with refralone and amiodarone for 60 minutes.

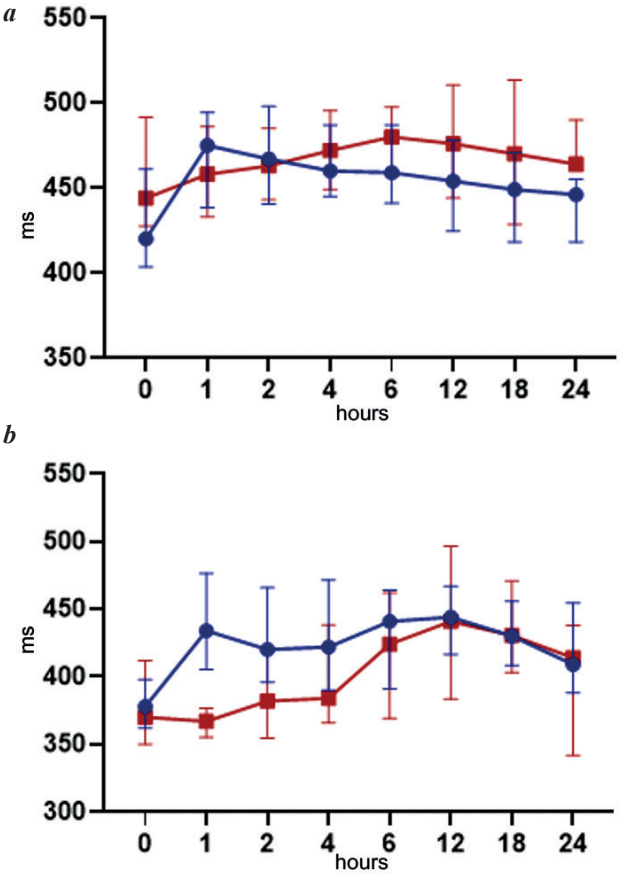

Fig. 4. Dynamics of the QTc (f) and QT (b) intervals after refralon and amiodaron administration. Note: blue line - refralon, red line - amiodarone.

Among the included patients, the median duration of the current paroxysm was 36 [21;138] hours and did not differ significantly between the comparison groups. The number of patients with paroxysm duration less than 24 h and more than 24 h in the analyzed groups was also comparable (see Table 1). Thus, although spontaneous recovery of SR in a number of included patients is possible, we consider the influence of this factor on the performance indicators to be insignificant.

DISCUSSION

The results of the study demonstrate that while being more effective, refralone is not inferior to amiodarone in terms of the safety criteria used. No life-threatening complications were reported in any patient during the study. Due to the effects on calcium channels and the beta-adrenergic blocking activity of amiodarone, the development of bradysystole during pharmacologic cardioversion is not uncommon. The incidence of bradycardia on the background of drug administration reaches 20% [12]. In our study, the rhythm-suppressing ability of the drug was also observed, and the development of clinically significant bradysystole (<50 beats/min) was reported in one patient (3.3%). According to the data of previous studies, bradyarrhythmias are the most frequent undesirable effect also when using Refralon, but all cases of bradyarrhythmias were noted after AF control and were represented by postconversion pauses and/or periods of sinus bradycardia, no episodes of excessive decrease in HR against the background of persistence of AF, which required discontinuation of the drug, have been described to date [13].

In addition to decreased ventricular contractions, arterial hypotension due to negative inotropic and vasodilatory effects is a frequent complication of amiodarone use. The incidence of arterial hypotension during intravenous administration of amiodarone reaches 30% of cases [14]. In our study, 2 (6.7%) patients had a decrease in blood pressure during stage 1 (rapid) infusion of the drug. The lack of effect on blood pressure during drug-induced cardioversion is undoubtedly the most important advantage of refralone. Attention should be paid to the fact that the observed undesirable effects determined the need to discontinue the drug infusion and, thus, determined the lower efficacy of amiodarone.

Given that refralone and amiodarone belong to class III of antiarrhythmic agents, prolongation of the QT interval was an expected adverse event. For example, excessive QT interval prolongation >500 ms was observed with an equal probability of 6.7% in the comparison groups. In the refralone group, QT prolongation>500 ms was noted after administration of the drug at doses of 20 μg/kg and 30 μg/kg. Excessive prolongation of the QT interval is known to increase the risk of dangerous ventricular tachycardia of the TdP type. According to literature data, during intravenous administration of amiodarone the development of ventricular arrhythmias is rare, within 1% of cases, but even after a single infusion the drug can significantly prolong the QT interval [14, 15]. Refralone also prolongs this interval, with an incidence of serious ventricular adverse events of 1.7% [13].

On this basis, the effect of refralone and amiodarone on the dynamics of QT and QTc intervals during the day af-

ter cardioversion was analyzed to identify the increased risk of life-threatening ventricular arrhythmias at a certain time. The fact that QT interval prolongation occurs in the first hours after refralone administration is also significant, as it indicates the highest DIC procedure and a decreased risk of their development by the end of 24 hours of follow-up.

Differences in QT/QTc interval dynamics also suggest a potentially lower likelihood of adverse drug interactions when maintenance antiarrhythmic therapy is administered for prolonged retention of restored SR after refralone administration compared with amiodarone, but confirmation of this assumption requires an appropriate clinical trial.

It should be emphasized that when using refralone at a minimum dose of 5 μg/kg, no adverse events selected as safety criteria were reported in any patient, with the efficacy of this dose being 56.7%. High efficacy with sufficient safety of the lowest dose makes it possible to study the use of the drug in the prehospital phase of treatment, but a separate clinical trial is needed to confirm this assumption.

CONCLUSION

1. The results of this study indicate the superiority of refralone over amiodarone not only in terms of the rate of SR recovery, but also in terms of the time to recover from paroxysms of Af/AFt.
2. The safety of ICV using refralone is not inferior to cardioversion with amiodarone, which gives grounds for expanding the use of the domestic antiarrhythmic drug in paroxysms of AF and AFt.

REFERENCES

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal*. 2021; 42(5): 373-498. https://doi.org/10.1093/eurheartj/ehaa612

2. Shkolnikova MA, Jdanov DA, Ildarova RA, 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. https://doi.org/10.11909/j.issn.1671-5411.2020.02.002.

3. Lip GY, Hee FL. Paroxysmal atrial fibrillation. *QJM: monthly journal of the Association of Physicians*. 2001;94(12): 665-678. https://doi.org/10.1093/qjmed/94.12.665.

4. Turakhia MP, Guo JD, Keshishian A, et al. Contemporary prevalence estimates of undiagnosed and diagnosed atrial fibrillation in the United States. *Clinical Cardiology*. 2023;46(5): 484-493. https://doi.org/10.1002/clc.23983.

5. Tuseth V, Jaatun HJ, Dickstein K. Amiodarone infusion in the treatment of acute atrial fibrillation or flutter: high versus low dose treatment. *Heart (British Cardiac Society)*. 2005;91(7): 964-965. https://doi.org/10.1136/hrt.2004.049171.

6. Cybulski J, Kułakowski P, Budaj A, et al. Intravenous amiodarone for cardioversion of recent-onset atrial fibrillation. *Clinical Cardiology*. 2003;26(7): 329-335. https://doi.org/10.1002/clc.4950260707.

7. Arakelyan M.G., Bockeria L.A., Vasilieva E.Yu., et al. Clinical guidelines for Atrial fibrillation and atrial flutter. *Russian Journal of Cardiology*. 2021;26(7): 190-260. (In Russ.) https://doi:10.15829/1560-4071-2021-4594.

8. Mironov NYu, Yuricheva YuA, Vlodzyanovskiy VV, 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): 193-199. (In Russ.) https://doi:10.20996/1819-6446-2021-03-05.

9. Gagloeva DA, Dzaurova HM, Zelberg MA, et al. Preliminary results of a prospective randomized study comparing the efficacy and safety of refralon and amiodarone in cardioversion in patients with paroxysmal atrial fibrillation and flutter. *Cardiovascular Therapy and Prevention*. 2023;22(4):3527 (In Russ.) https://doi:10.15829/1728-8800-2023-3527.

10. Pluymaekers N a. HA, Dudink E a. MP, Weijs B, et al. Clinical determinants of early spontaneous conversion to sinus rhythm in patients with atrial fibrillation. *Netherlands Heart Journal*. 2021;29(5): 255-261. https://doi.org/10.1007/s12471-020-01528-5.

11. Leonova MV. Drug-induced arrhythmias. *Meditsinskiy sovet = Medical Council.* 2020;(21): 26-40. (In Russ.). https://doi.org/10.21518/2079-701X-2020-21-26-40.

12. Mironov NYu, Yuricheva YuA, Vlodzyanovskiy VV, et al. Safety and Effectiveness of Pharmacologic Conversion of Atrial Fibrillation and Flutter: Results of Multicenter Trial. Part II: Assessment of Safety. *Rational Pharmacotherapy in Cardiology*. 2021;17(5): 668-673 (In Russ.) https://doi.org/:10.20996/1819-6446-2021-10-06.

13. Kowey PR, Marinchak RA, Rials SJ, et al. Intravenous amiodarone. *Journal of the American College of Cardiology*. 1997;29(6): 1190-1198. https://doi.org/10.1016/s0735-1097(97)00069-7.

14. Friedman A, Miles J, Liebelt J, et al. QT Dispersion and Drug-Induced Torsade de Pointes. *Cureus*. 13(1): e12895. https://doi.org/10.7759/cureus.12895.