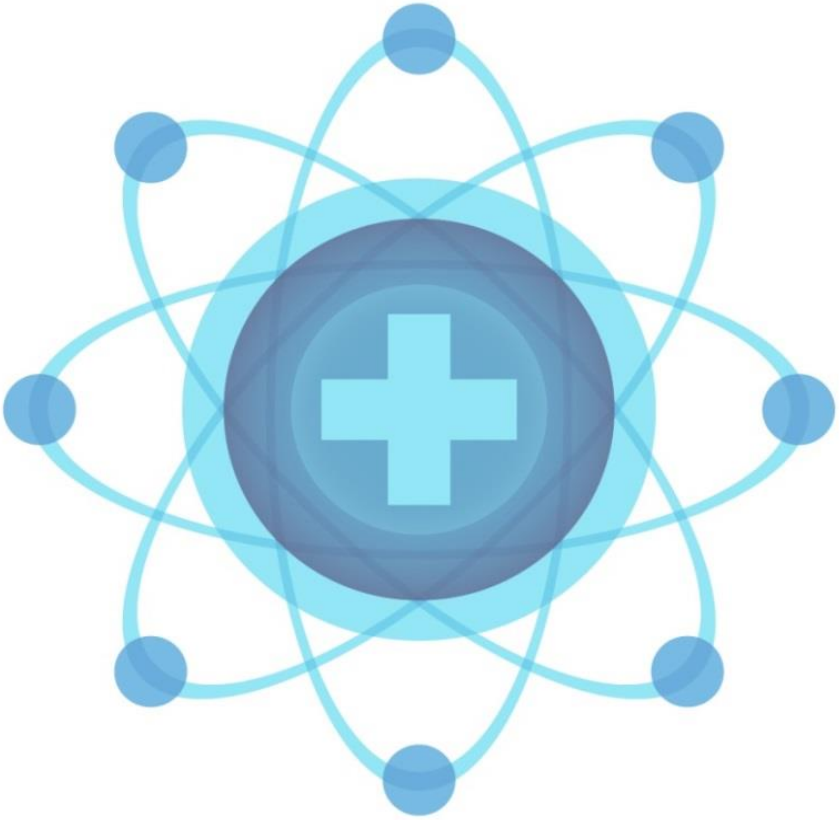

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Comparative effectiveness of propafenone and aksaritmin for conversion of paroxysmal atrial fibrillation

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Atrial fibrillation (AF) is one of the most common forms of arrhythmias, occurring in the general population in up to 2% of cases. The probability of the development of AF increases with age. AF is detected in 3.8% of individuals older than 60 years and in 9% of people older than 80 years [1]. AF is the cause of 20–30% of all strokes [2, 3]. In addition, undiagnosed ("silent") AF may be the cause of some cases of "cryptogenic" strokes [4, 5]. Paroxysmal AF increases the risk of stroke to the same degree as other forms of AF (persistent or permanent) [6].

Propafenone (Pr), an IC class drug, has a high efficiency in restoration of sinus rhythm (SR) in patients with paroxysms of AF and a fairly fast action. A series of controlled trials in patients with recent-onset AF without heart failure who were hospitalised with enforced bed rest has shown that orally taken propafenone (450 to 600 mg as single dose) exerts a relatively quick effect (within 3 to 4 hours) and a high rate of efficacy (72 to 78% within 8 hours) [7]. Such method of using propafenone was called the "pill in the pocket". Considering more high risk of side effects of the drug when taken in a higher dose, the use of "pill in pocket" strategy is recommended only if safety of taking a larger dose of the drug was previously evaluated in a hospital.

In Uzbekistan, beside propafenone, the treatment (pharmacological cardioversion) AF is held with such antiarrhythmic drugs (AADs) as dietilaminopropioniletoksikarbonilaminofenotiazin hydrochloride (ethacizine), lappaconitine (allapinin), amiodarone. Verkalant is not registered. Among these drugs, allapinin is distinguished by plant origin. After per os administration of allapinin in patients with AF naturally decreases in the frequency of atrial impulses up to transformation into atrial flutter (AF) (in 14% of cases), after which in 71% cases, sinus rhythm is restored [12]. Allapinin was included in national and Euroasian guidelines for preventing of AF and restoring SR. However, in some cases (18–65%), there are side effects from central nervous system (dizziness, headache, diplopia), which are limited the scope of its administration and require refusal to take the drug up to 10% of cases [8, 9]. In this regard, scientific and practical interest introduces a new AAD – aksaritmin (Aks). Aks was developed by the Institute Chemistry of plant substances named after S.Yu.Yunusov of Academy of Sciences of the Republic of Uzbekistan. It is the sum of nine alkaloids, similar in chemical structure to lappaconitin (allapinin). Aks is obtained from the roots and rhizomes of the Aconitum septentrionale. The technology for its production is much simpler, and the economic cost of obtaining raw materials is 2 times lower than that of allapinin [10,11].

It is recognised, that the composition of allapinin mainly contains lappaconitine (up to 80%). The content of N-deacetyllappaconitine (the main metabolite of lappaconitine, which is not inferior to the latter in activity, but is less toxic) in the

composition of allapinin does not exceed 5%. In the composition of aksaritmin, the proportion of lappaconitine is less - about 40-60%, while the proportion of N-deacetyllappaconitine is greater than that of allapinine - about 10-20%. Due to this ratio of components, in various experimental models of cardiac arrhythmias, Aks, according to the developers, showed less toxicity and greater therapeutic latitude [10,11].

Purpose: Evaluation of comparative effectiveness of propafenone and aksaritmin for conversion of atrial fibrillation (AF) in patients without/minimal structural heart disease (ejection fraction is more than 50%).

Materials and methods: The study was conducted as part of the research work of the Heart arrhythmias department. The study included 60 patients (31 men), mean age - 55.3±11.9 y.o. ***The inclusion criteria*** for patients in the study were: hemodynamically stable symptomatic paroxysmal AF (mean duration–16.3±9.1 hours) who did not have pronounced structural changes in the myocardium and gave written informed consent for inclusion in the study. ***Exclusion criteria from the study:*** age of patients under 18 and over 80 years of age, acute myocardial infarction and postinfarction cardiosclerosis, unstable angina pectoris, chronic heart failure III-IV functional class according to NYHA, ejection fraction (LVEF) less than 50%, sick sinus syndrome, AV block II-III degrees, left ventricular hypertrophy ≥ 14 mm, hepatic and renal failure and other concomitant diseases in the stage of decompensation, pregnancy and lactation, taking other AADs.

All patients at the beginning of the study underwent electrocardiography (ECG), including acute drug test, echocardiography (Echo), Holter ECG monitoring (HMECG), ultrasound of the liver and kidneys, biochemical blood test (lipid spectrum, coagulogram, blood glucose, ALT, AST, bilirubin, urea, creatinine, TSH, free T4, rheumatoid factor, C-reactive protein, ASLO, and electrolytes) to exclude concomitant conditions potentially generating various cardiac arrhythmias. Given the conditional belonging of Aks to the IC class of antiarrhythmic drugs, special attention was paid to Echo parameters. In addition to Aks, patients were prescribed standard therapy in accordance with the underlying disease.

The patients were divided into two groups (they did not differ in the main clinical and anamnestic characteristics): 1-group (n=30), Pr was prescribed in dose 450-600 mg per os; 2-group (n=30), Aks was prescribed in dose 50 mg per os (in combination with beta-blockers (60%) in cases of tachysystole (≥ 140 b.p.m.)). Two groups were also comparable in terms of age, gender, underlying disease and EchoCG parameters (Table 1).

Table 1. Baseline characteristics.

Parameters	**Data**	
	1st group (Aks)	**2nd group (Pr)**
Number of patients, n	**30**	**30**
Age, years	**55,7±11,8**	**54,6±13,1**

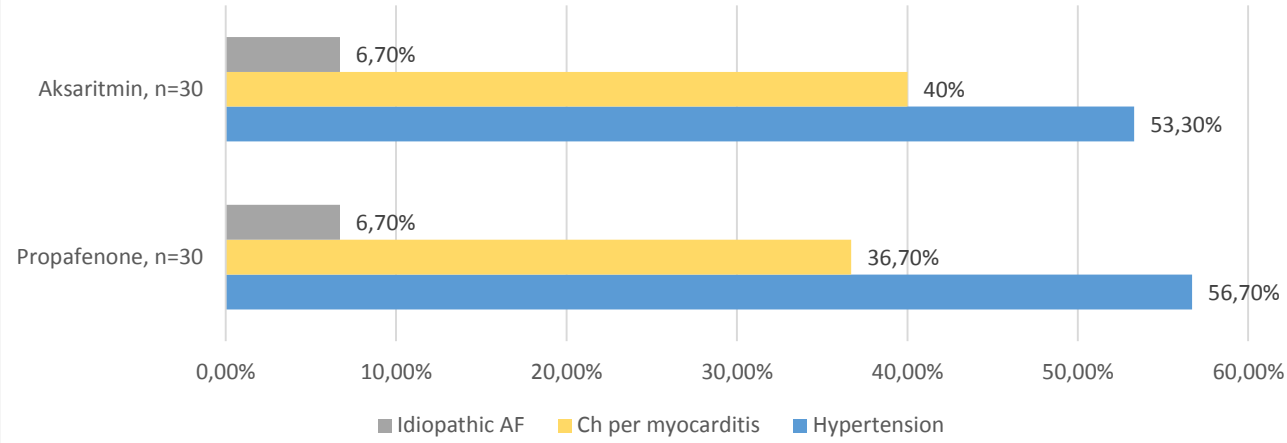
Male, n (%)	**16 (53,3%)**	**15 (50%)**
History of AF, months	**17.3±3.8**	**18.2±4.7**
BMI, kg/m2	**27,8±4,0**	**27,6±5,6**
Mean CHA2DS2-VASc score	**1.8 (0.7)**	**1.7 (0.7)**
LA, mm	**35,1±4,8**	**33,9±5,9**
EF, %	**63,6±4,4**	**64,9±4,0**
MR		
Mild	**14 (46,7%)**	**12 (40%)**
Moderate	**0**	**0**
Severe	**0**	**0**
Medications at baseline		
Anticoagulant (%)	**10 (33,3%)**	**9 (30)%**
Aspirin (%)	**17 (56,7%)**	**18 (60%)**
Clopidogrel (%)	**1 (3,3%)**	**2 (6,7%)**
ACEI/ARB (%)	**24 (80)%**	**25 (83,3%)**
Beta blocker (%)	**21 (70%)**	**20 (66,7%)**
CCB (%)	**2 (6,7%)**	**3 (10%)**
Digoxin (%)	**0**	**0**

BMI, body mass index; LVEF, left ventricular ejection fraction; LA, left atrial; MR, mitral regurgitation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Statistical analysis was carried out by the STATISTICA 13. Differences were considered statistically significant at $p<0.05$.

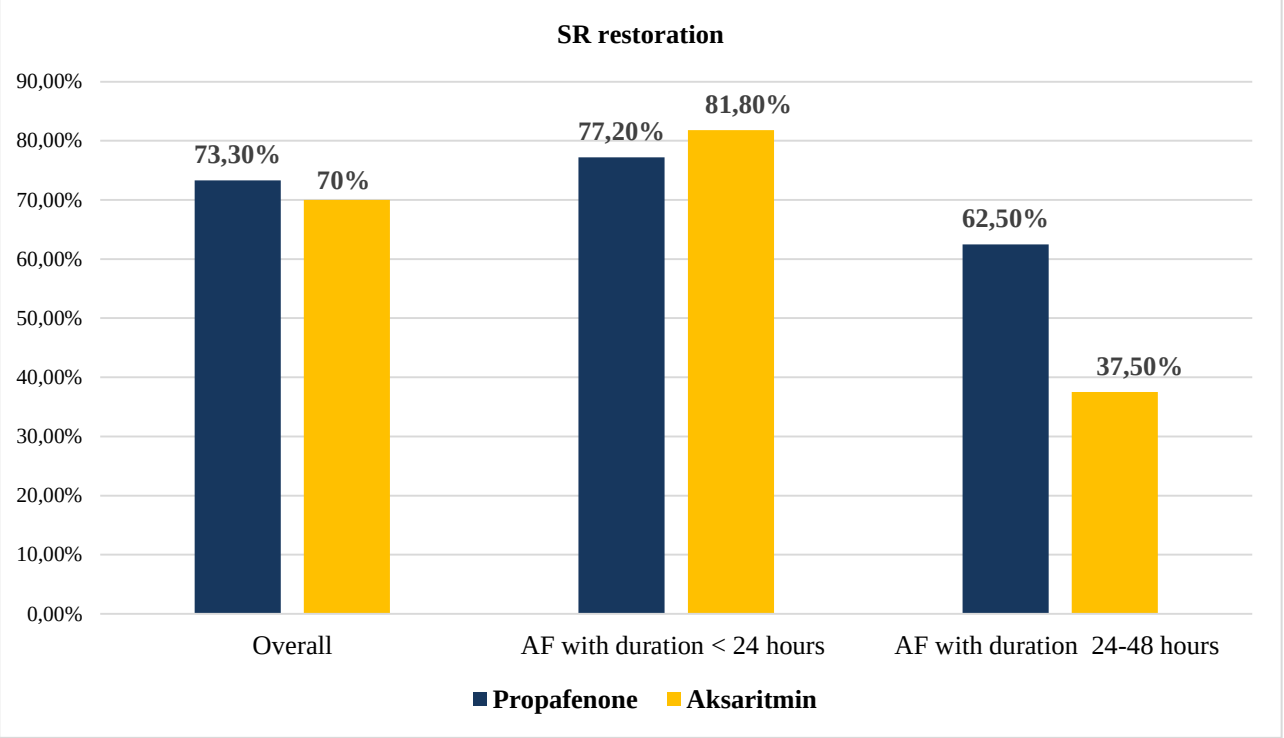
Results: The main causes of AF in group 1 and group 2: hypertension - 17 (56.7%) and 16 (53.3%), chronic persistent myocarditis - 11 (36.7%) and 12 (40%), idiopathic AF - 2 (6.7%) and 2 (6.7%) patients, respectively.

Figure 1. Main etiological causes of AF.



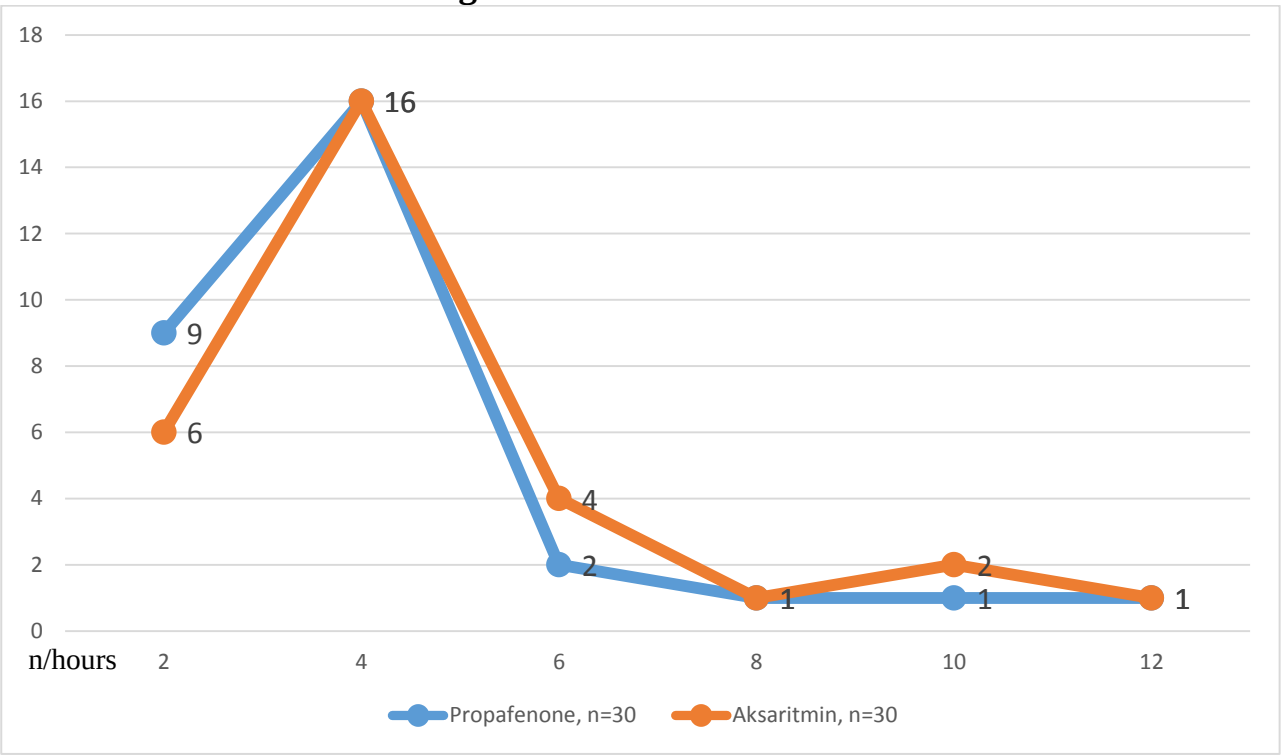
The anamnesis of AF averaged 17.3±3.8 months in gr 1 and 18.2±4.7 months in gr 2. In Pr group according to the above-described scheme ("pill in a pocket"), sinus rhythm was restored in 22 (73.3%) of 30 patients, and the mean time to restore the sinus rhythm was 4.12±3.87 hours (figure 2) from the start of therapy. At the same time, the effectiveness of Pr in patients with a paroxysm duration of less than 24 hours was 77.2% - in 17 patients out of 22, whereas in patients with a duration of AF 24-48 hours it was 62.5% - 5 patients out of 8.

Figure 2. Effectiveness of Pr and Aks.



Aks restored sinus rhythm in 21 (70%) out of 30 patients ($\chi 2=0.082$; $p>0.05$), and the mean restoring time of sinus rhythm was 4.63±4.33 hours from the start of therapy ($p>0.05$). At the same time, the effectiveness of Aks in patients with a paroxysm duration of less than 24 hours was 81.8% - in 18 patients out of 22 ($\chi 2=0.140$; $p>0.05$), with a duration of more than 24-48 hours it was 37.5%-3 patients out of 8 ($\chi 2=1.000$; $p>0.05$) (figure 3).

Figure 3. Time to cardioversion.



ECG parameters such as the width of the QRS complex and the QT interval were evaluated to assess the safety of drugs (other parameters were not taken into account due to the non-sinus nature of the rhythm). Against the background of established doses of drugs (for Pr 450-600 mg and for Aks 50 mg), changes in the QRS complex were +13.3% (from 65.2 ms to 73.9 ms) in case of Pr and +10.1% (from 67. 4 ms to 74.2 ms) in case of Aks ($p>0.05$). At the same time, the QT interval lengthened by 7.2% (from 330.5 ms to 354.4 ms) while taking Pr and by 4.6% (from 339.2 ms to 354.7 ms) while taking Aks ($p >0.05$).

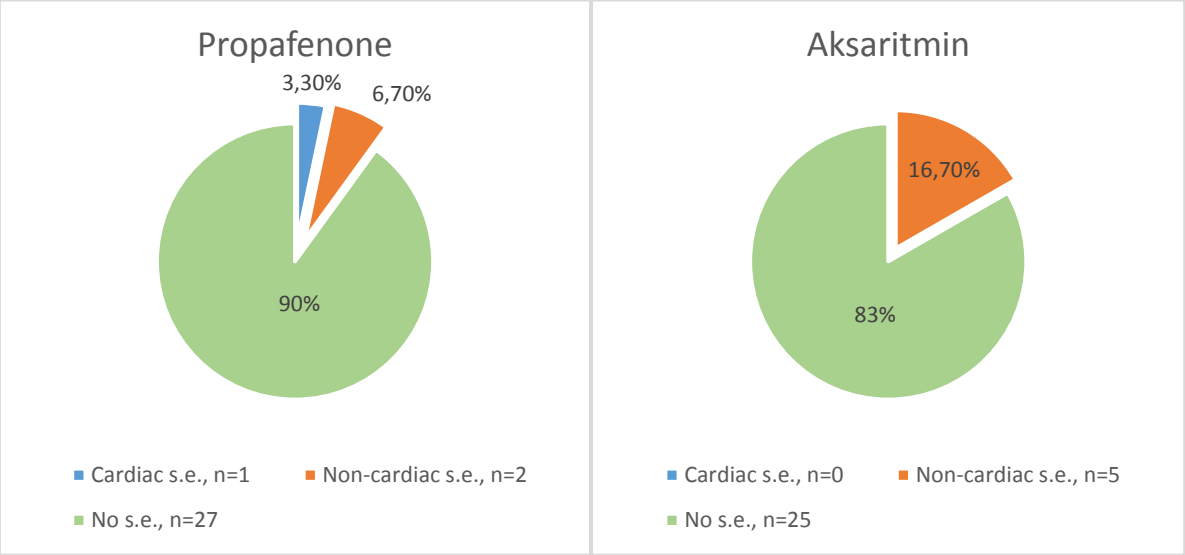
Table 2. Changes in ECG parameters due to propafenone and aksaritmin.

Parameters	Propafenone (450-600 mg)			Aksaritmin (50 mg)		
	Initially	After 8 hours	Changes in %	Initially	After 8 hours	Changes in %
QRS, ms	65,2	73,9	+13,3	67,4	74,2	10,1
QT, ms	330,5	354,4	+7,2	339,2	354,7	+4,6

Side effects of varying severity were observed during drug administration. They can be conditionally divided into 2 types: cardiac (hypotension, bradycardia, and others) and non-cardiac (dizziness, headache, impaired gaze fixation, nausea). Thus,

in the Pr group, 1 patient (3.3%) had hypotension (90/60 mmHg) and bradycardia (50 bpm, after restoration of sinus rhythm), in two patients (6.7%) there was nausea. In the Aks group cardiac side effects were not observed, while the incidence of non-cardiac side effects was higher (16.7%).

Figure 4. Side effects.



Conclusion:

Pr and Aks practically did not differ in efficiency (73.3% and 70%, respectively) and in the time of relief (4.12±3.87 h and 4.63±4.33 h, respectively) of AF paroxysms. At the same time, Aks (including combination with beta-blockers) seems little bit preferable for relief of AF with a duration of up to 24 hours - 81.8% versus 77.2% ($p>0.05$), and Pr was more preferable for relief of AF with a duration of 24-48 hours - 62.5% versus 37.5% ($p>0.05$). Aks is relatively new and promising drug for the treatment of patients with new onset paroxysmal AF. Our results could induce larger investigation for determination of efficacy and safety of Aks in patients with paroxysmal AF.

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