**UCD** 616.125-008.318-008.9:615.22
**DOI** 10.17802/2306-1278-2022-11-1-17-25

# THE POSSIBILITY OF USING PHARMACOLOGICAL ANTIARRHYTHMIC THERAPY AND MODULATED KINESOTHERAPY AS A PRIMARY PREVENTION OF ATRIAL FIBRILLATION IN PATIENTS WITH METABOLIC SYNDROME AND WITH PREMATURE ATRIAL COMPLEXES: PROSPECTIVE STUDY

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ORIGINAL STUDIES

**Highlights**

• The results of primary prevention of atrial fibrillation by using antiarrhythmic drug therapy and modulated kinesotherapy in patients with metabolic syndrome with premature atrial complexes are presented.

• A significant decrease in the development of the disease was revealed in patients with metabolic syndrome and risk of atrial fibrillation within a year after the examination with the help of pharmacological antiarrhythmic therapy of atrial ectopia and modulated kinesotherapy as primary prevention in comparison with therapy aimed at correcting blood pressure, glucose and blood lipids.

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| **Aim** | To assess the possibility of using antiarrhythmic drug therapy (DT) and modulated kinesotherapy (MK) in patients with metabolic syndrome (MS) and premature atrial complexes (PAC) as the primary prevention of atrial fibrillation (AF). |
| **Methods** | 426 MS patients with PAC aged from 58 to 72 (mean 66.4±0.7 years old) were included in the study. All patients had a high probability of developing primary AF within 1 year after the enrollment. Antiarrhythmic DT with class I–III drugs was used as the primary prophylaxis of AF in 149 (34.97%) patients, MK – in 121 (28.40%), the correction of blood pressure, glucose and blood lipids – in 156(36.63%). All patients were followed up for one year and the end point of observation was the maintenance of sinus rhythm or AF registration. |
| **Results** | Various clinical forms of AF were recorded in 26.45, 31.54% and 95.51% of patients with MS during primary prevention with the help of pharmacological AAT, MK and correction of its potentially modifiable components (arterial pressure, glucose and blood lipids), respectively, during a ayear after the examination. |
| **Conclusion** | The use of both antiarrhythmic DT of I–III classes, and MK as a primary prophylaxis of AF in patients with MS with PAC and the risk of AF development within one year after the first examination made it possible to reduce the frequency of the arrhythmia by the correction of blood pressure, glucose and blood lipids. |

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|---|---|
| **Keywords** | Metabolic syndrome • Primary prevention • Atrial fibrillation • Antiarrhythmic therapy • Modulated kinesitherapy |

***Received:*** *07.11.2021;* ***received in revised form:*** *27.12.2021; 19.01.2022;* ***accepted:*** *04.02.2022*

**Список сокращений**

AAT – antiarrhythmic therapy
AF – atrial fibrillation
BMI – body mass index
BP – blood pressure
ECG – electrocardiogram
EDV – end diastolic volume
LA – left atrium
MK – modulated kinesotherapy
MS – metabolic syndrome

## Introduction

Atrial fibrillation (AF) once developed in patients with metabolic syndrome (MS) almost always recurs eventually turning into a permanent form. Primary prevention is the main way to avert this arrhythmia in patients with MS [1]. Correction of potentially

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modifiable components of MS, as well as predictors of its development, such as premature atrial contractions, is used as the primary prevention of AF. To influence the components of MS various types of physical activity are most often used [1, 2]. One of the types of aerobic exercise is modulated kinesotherapy (MK), which is the patient's walking in accordance with the heart rate [3]. A positive effect of the use of MK and beta-blockers in MS patients without cardiac arrhythmias as a primary prevention was previously revealed when a high risk of AF was detected [4, 5]. In patients with MS and ectopia cordis the value of the prognostic index of the development of AF <1.5 units indicated a high risk of developing the disease within a year after examination [6, 7]. It can be assumed that an increase in the prognostic index, for example, if to use MK and drug antiarrhythmic therapy (AAT) or other methods of treatment in MS patients, in comparison with the initial data, serves as a potential criterion for the effectiveness of primary arrhythmia prevention before getting a positive clinical result. However, in the literary sources there are no data on the use of AAT and MK as primary prevention in identifying a high risk of AF in patients with MS and premature atrial complexes.

**The aim o f the study** is to evaluate the possibility of using AAT and MK in MS patients with premature atrial complexes for primary prevention of AF.

## Materials and Methods

426 MS patients aged 58 to 72 were observed (mean age 66.4±0.7) in North-Western State Medical University named after I.I. Mechnikov. All patients had a risk of developing primary AF within a year after the inclusion in the study. The number of men was 186 (43.66%) and 240 (56.34%) women (p>0.05). MS was diagnosed according to generally accepted criteria.

After a clinical and instrumental examination, which included an echocardiographic examination, daily monitoring of an electrocardiogram (ECG), registration of a signal-averaged ECG, etc., the criteria for inclusion in the study were determined. Techniques and hardware for detecting contractility and dysfunction of the left ventricle, the volume of the heart chambers, as well as the prognostic index of the AF development, functional class of heart failure (6-minute walk test), average blood pressure (BP) were described earlier [4–7]. The prognostic index of the development of AF was calculated by the formula: (A÷B) x (C÷N) , where A and B are the duration of the filtered wave P and the dispersion of the wave P, determined according to the signal-averaged atrial ECG and daily ECG monitoring, respectively (ms); C is the linear deviation of the corrected coupling interval of premature atrial complexes; N is the number of premature atrial complexes used for the study (number/hour) [6, 7]. To exclude false positive results of determining the prognostic index of AF development, the corrected pre-ectopic interval of premature atrial complexes was analyzed in at least 20 supraventricular ectopias. The index of ≤1.5 units in MS patients with premature atrial complexes indicated the occurrence of arrhythmia within a year after the examination [6, 7]. It should be noted that the detection of atrial ectopia identifies the potential risk of developing primary AF in patients with MS and an indefinite realization in time, and the number of extrasystoles per day or hour of observation does not reflect the degree of risk of arrhythmia [1, 2, 6, 7].

The criteria for inclusion in the study were sinus rhythm, subjective sensation of premature atrial complexes, chronic heart failure of functional class I-II according to NYHA, absence of AF registration during at least 4-5 procedures of daily (1–3 days) ECG monitoring at least once every 1–2 weeks during 2–3 months, left ventricular ejection fraction ≥54% [4, 5], prognostic index of AF development ≤1.5 units, informed consent of the patient for examination and treatment [4–7]. Patients with cardiomyopathies, heart defects and other diseases presented in previously published papers were excluded from the study [4, 5, 7].

Hypertension was detected in 358 (84.04%) of the examined patients, diabetes mellitus in 297 (69.72%), and chronic obstructive pulmonary disease in 96 (22.54%). Correction of blood pressure with hypotensive drugs, such as indapamide, telmisartan, valsartan, was applied to all patients. In addition to the diet, hypoglycemic and hypolipidemic drugs were used to normalize blood glucose and lipids. Correction of potentially modifiable components of MS was prescribed as a basic therapy.

All patients underwent medical AAT along with the basic one. In case of unwillingness of a patient to receive pharmacotherapy or with the development of side effects and contraindications MK was performed. In case of a negative reaction of the examined person to the use of antiarrhythmic drugs or MK only basic therapy was used. These patients made up the control group.

At first, all the patients were treated with class II drugs if any effect was absent, class I or III drugs, such as metoprolol, propranolol, carvedilol, allapinin, etacizine, propafenone, sotalol in moderate therapeutic doses were used with the exception of amiodarone, the drug which is used for depression of the contractility of the heart [2]. Before and after pharmacological antiarrhythmic therapy carried out from 3–4 to 7 days, the prognostic index of the development of AF was determined. The criterion for a positive effect was an increase in the indicator in the comparison with the initial values [8].

Modulated kinesotherapy consisted of a patient's walking in accordance with the frequency of the heart rate [3, 4]. At the first stage MK was applied twice a day

or more for 30–60 minutes during 5–7 days. When a positive effect was detected, determined by an increase in the prognostic index of AF development in the comparison with the initial data, MK was performed daily for at least 150 minutes per day [9].

The development of AF during the year of observation was the end point of the study. The occurrence of AF was the basis for anticoagulants (dabigatran, rivaroxaban and others) subscription [1, 2]. All studies were performed on the sinus rhythm at least once every 1–2 months. When AF (paroxysmal or persistent form) appeared, the examination was performed after the first attack was stopped and in case of pharmacological cardioversion in 5–7 half-lives periods after antiarrhythmic drugs were used to stop the arrhythmia.

The study was performed in accordance with the standards of Good Clinical Practice and the principles of the Helsinki Declaration. All the participants gave the written informed consent to be included in the study.

### Statistical Analysis

Statistical processing of the obtained data was performed using the computer program Statistica, version 11.0 (StatSoft Inc., USA). The average values and its error (M±m), standard deviation (σ), 95% confidence interval of the average values, Student and Pearson criteria were used. Verification of the distribution normality of the studied quantitative indicators was evaluated using the Kolmogorov -Smirnov criterion and according to the ±3σ rule (Gauss distribution), comparison of two binary variables by the method of multiple logistic regression with the determination of the odds ratio (OR) and its standard error (SE). The values of $p<0.05$ were considered statistically significant.

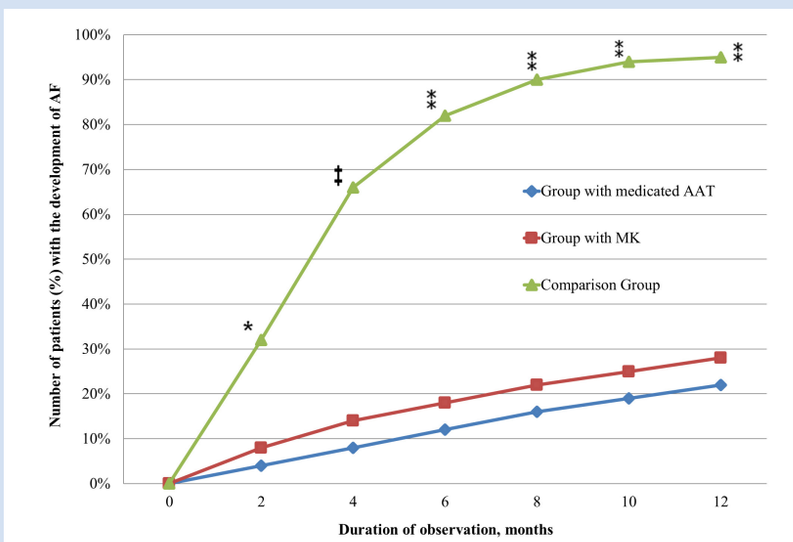
## Results

149 (34.97%) patients underwent AAT, 121 (28.40%) had MK, 156 (36.63%) had blood pressure correction, glucose and lipids (comparison group). There was no significant difference among the groups by gender, age, concomitant diseases, results of clinical, laboratory and instrumental examination.

Propranolol was the most effective for 33 (22.15%) patients in the drug AAT group, metoprolol – for 47 (31.54%), carvedilol – for 26 (17.45%), etacizine – for 15 (10.07%), allapinine for 10 (6.71%), propafenone- for 8 (5.37%), for the rest – sotalol. There was no significant difference in the studied indicators in patients included in the comparison groups, drug-induced AAT and MK (table).

Within a year after the first examination, paroxysmal and persistent forms of AF were registered in 32 (26.45%), 47 (31.54%) and 149 (95.51%) patients with drug-induced AAT, MK and comparison groups, respectively ($p<0.05$), and in the latter there was a statistically significant increase in cases of AF (*Figure*). The risk of AF increased in patients over 65 years old (odds ratio (OR) 8.93, SE 0.94), with body mass index (BMI) values >35 kg/m$^2$ (OR 5.5, SE = 0.92), with an index of the final diastolic volume of the left atrium (CDL) ≥37 ml/m$^2$ (OR 5.8, SE 0.92), E/A ratio <0.8 (OR 2.5, SE 1.3), prognostic index of AF development <1.5 units (OR 12.8, SE 1.6).

A year after the first examination, patients in the comparison group showed a significant decrease in the left ventricular ejection fraction, the E/A ratio, the prognostic index of AF development, the values of the 6-minute walk test and an increase in the EDV LA index, the number of premature atrial complexes/hour, average blood pressure and BMI compared with the data when included in the study (see the *table*). In the group of patients with drug-induced AAT, a statistically significant increase in the prognostic index of AF development and a decrease in the number of premature atrial complexes were determined, in patients receiving MK, a statistically significant increase in the left ventricular ejection fraction, the E/A ratio, the prognostic index of AF development, the values of the 6-minute walk test and a significant decrease in the EDV LA index, the number of premature atrial complexes, average blood pressure and BMI in comparison with baseline data. The rest of the indicators in patients of the studied groups did not significantly




Cumulative proportion of patients (in %) with AF in the drug antiarrhythmic therapy and MK group

***Note:*** ** – statistically significant difference in indicators of the drug antiarrhythmic therapy group when correlated with the comparison group at p<0,05; ‡ – at p<0,01; ‡‡ – at p<0,001; † – with the MK group at p<0.05; AAT – antiarrhythmic therapy; AF – atrial fibrillation; MK – Modulated kinesitherapy.*

differ in comparison with the results when the patients were included in the study (see the *table*).

The positive effect of using medicamentous AAT and MK as primary prevention of AF in MS patients was associated with an increase in the prognostic index of AF development >1.5 units (OR 12.1, SE 0.94), to a less extent – with a decrease in the number of atrial ectopias per day of observation (OR 0.89, SE 1.1).

## Discussion

For the early diagnosis of AF, all patients, especially the older age group, are recommended to assess the regularity of the pulse with the determination of both palpation and the use of automatic or semi-automatic tonometers, followed, if necessary, by ECG registration on a smartphone or when contacting medical institutions [10]. In recent years, MS patients with indicators on the $CHA_2DS_2$-VASc risk scale for thromboembolic complications ≥1 and ≥2 points for men and women, respectively, have been included in the high-risk group for AF development: daily monitoring of pulse regularity is recommended for these patients, and with an increase in the number of points on this scale, the frequency of detection of AF increases significantly [11, 12].

In recent years at least 21 risk stratifications, including Framingham scales (1994–2014), have been proposed to assess the risk of developing the first episodes of AF including MS patients [13]. A meta-analysis of risk stratifications (during a retrospective study) showed that the CHARGE-AF system is the most informative for the five-year prediction of the first AF attacks [14], which includes simple and publicly available indicators such as age, gender, anthropometric parameters and blood pressure level [13]. The accuracy of the five-year primary prediction of AF using CHARGE-AF, according to a retrospective analysis, averaged 50%. It should be noted that almost all patients with MS, especially those over 60, have a high or very high five-year probability of developing AF if to use the CHARGE-AF model [14].

Currently, the mechanisms of AF development in MS patients are insufficiently studied [1]. In recent years, the theory of AF induction as a result of atrial cardiomyocytes overload with $Ca^{++}$ ions into the diastole due to the development of oxidative stress has been widespread [1]. This process causes the occurrence of atrial ectopias due to activation of trigger mechanisms and/or re-entry in the region of the posterior wall of the left atrium and leads to AF with its subsequent recurrence and/or transition to a permanent form [1]. It should be noted that in MS patients with AF the formation of an ectopic focus in the atria and/or pulmonary veins is rarely observed [1, 2].

In most cases, premature atrial complexes in patients with MS are regarded as ectopia with a potentially favorable course, often not requiring medicamentous AAT, except for the presence of a subjective feeling of extrasystole [1, 2]. On the other hand, in these patients, persistent and/or recurrent supraventricular ectopia can independently or indirectly induce the violation of the excitation conduction along the atrial

The state of some clinical and instrumental parameters, predictive index for the development of AF in patients of drug antiarrhythmic therapy and MK groups when they were included in the study (A) and one year after the first examination (B)

| Parameter | Comparison Group, n = 156 | | Group with medicated AAT, n = 149 | | Group with MK, n = 121 | |
|---|---|---|---|---|---|---|
| | A | B | A | B | A | B |
| LVEF, % | 61,84±0,57 (54–69) | 54,01±0,66† (46–62) | 61,54±0,52 (55–68) | 60,38±0,65 (52–70) | 61,47±0,61 (54–68) | 68,35±0,81‡ (59–77) |
| E/A. units | 0,95±0,02 (0,71–1,23) | 0,78±0,01† (0,61–0,95) | 0,94±0,01 (0,75–1,15) | 0,96±0,01 (0,84–1,08) | 0,94±0,01 (0,74–1,15) | 1,07±0,01† (0,92–1,21) |
| LAEDVI, mL/m² | 36,78±0,25 (34–39) | 41,93±0,57† (35–46) | 37,54±0,24 (33–41) | 37,53±0,23 (34–41) | 36,54±0,24 (32–42) | 32,53±0,43‡ (27–38) |
| PIDAF, units | 0,75±0,05 (0,01–1,49) | 0,07±0,01† (0,02–0,12) | 0,76±0,06 (0,02–1,50) | 4,17±0,34⁑ (0,42–8,12) | 0,76±0,06 (0,03–1,49) | 5,07±0,46⁑ (0,72–9,34) |
| Number of PAC/h | 172±6 (103–241) | 398±22† (126–687) | 182±7 (109–256) | 36±3⁑ (8–64) | 180±7 (98–263) | 33±2⁑ (9–58) |
| MAP, mmHg | 117±1 (103–131) | 121±1† (106–131) | 119±6 (102–132) | 116±1 (102–128) | 118±1† (104–131) | 105±1† (95–116) |
| 6-minute test, meters | 436,5±6,7 (365–510) | 375,7±5,1† (315–436) | 447,9±6,3 (372–516) | 442,7±6,7 (368–518) | 422,9±7,3 (358–489) | 546,5±9,8† (445–648) |
| BMI, kg/m² | 32,9±0,32 (30,3–35,4) | 35,9±0,33† (32,1–39,7) | 32,7±1,02 (30,1–35,1) | 33,1±0,34 (31,4–35,6) | 33,9±0,32 (31,5–36,2) | 28,4±0,24† (25,1–31,6) |

***Note:*** *1 – above M±m, below – 95% confidence interval of mean values; * – statistically significant difference in indicators in comparison with the control group at p<0,05; † – with the initial data at p<0.05; ‡ – at p<0,01; ⁑ – at p<0,001; AAT – antiarrhythmic therapy; BMI – body mass index; E/A – the ratio of the maximum velocities of blood flow through the mitral valve during diastole of the left ventricle (E) and atrial systole (A); LAEDVI – left atrial end diastolic volume index; LVEF – left ventricular ejection fraction; MAP – mean arterial pressure; MK – Modulated kinesitherapy; PAC – premature atrial complexes; PIDAF – predictive index for the development of atrial fibrillation.*

myocardium [1, 2]. However, the number of atrial extrasystoles per day of follow-up is not the main risk criterion for primary AF in patients with MS [1, 2, 6, 7].

The probability of AF was determined according to the prognostic index (an indicator of ≤ 1.5 units is associated with the occurrence of arrhythmia within a year after the examination) [6, 7]. To determine the prognostic index of the development of AF, the data from the signal-averaged ECG of the atria, the dispersion of the P wave and the analysis of the preectopic interval of premature atrial complexes were used [6, 7]. In MS patients, the risk of developing AF increases significantly with the age and BMI increasing, reaching about 90% in case of the prognostic index values decrease of AF development in comparison with baseline indicators (<1.5 units) [7].

The previously obtained data are consistent with the results of this study. In 26.45% and 31.54% of MS patients AF was registered ($p>0.05$) despite the use of MK in addition to basic medicamentous AAT as AF primary prevention . The positive effect of using these methods in MS patients was highly correlated with an increase in the prognostic index of arrhythmia development (>1.5 units). Thus, the progressive increase in the prognostic index values of AF development in comparison with the initial data may probably be a potential preclinical criterion reflecting the effectiveness of arrhythmia primary prevention in MS patients not only when using medicamentous AAT and MK but also other treatment methods. It should be noted that in all MS patients both without AF and with the development of arrhythmia with medication AAT and MC, a statistically significant decrease in the number of premature atrial contractions was observed in comparison with the baseline data (the difference between the positive result of arrhythmia primary prevention and a decrease in the number of supraventricular extrasystoles did not exceed 0.89). In this regard, a decrease in the number of atrial ectopias not only with medicamentous AAT and MK but also with other methods of treatment in MS patients cannot be a reliable criterion for the primary prevention effectiveness of AF.

Apparently the positive effect of medicamentous AAT is mainly associated with the elimination of electrophysiological mechanisms of premature atrial complexes development [2] since no significant changes in hemodynamic parameters, class of chronic heart failure, BMI before and after therapy were noted.

There are only few studies on the use of antiarrhythmic drugs in MS patients with atrial ectopias for the primary prevention of AF which is probably due to an increased risk of negative events in comparison with the predicted positive outcome of therapy [1, 2]. Medicamentous AAT carried out for the primary prevention of AF in MS patients with premature atrial complexes is usually used in identifying a high and very high risk of arrhythmia in particular from several months to a year [2]. In all MS patients along with a positive result of MK as a primary prevention of AF a decrease in the size of the heart chambers, left ventricular dysfunction and BMI was observed. The positive effect of MK was noted, firstly, due to a decrease in afterload, left ventricular dysfunction and left atrium volume, both due to a decrease in circulating blood volume as a result of BMI regression and arteriole dilation [1–3, 15]; secondly, due to the accumulation of protective stress proteins, an increase in the activity of prostaglanoids that limit activity sympathetic-adrenergic system, which increases the resistance of cardiomyocytes to the damaging effects of oxidative stress products [1, 2, 15].

## Conclusion

When conducting medical AAT and MK in MS patients for AF primary prevention when identifying the risk of its occurrence within a year after the examination, the disease was registered in 26.45% and 31.54% of patients respectively. Primary prevention in MS patients with atrial ectopias by the method of individualized medicamentous AAT and MK allowed to reduce the development of AF in three times more in comparison with the correction of blood pressure, glucose and blood lipids.

The value of AF prognostic index development of 1.5 units or more may probably be a potential preclinical parameter reflecting the effectiveness of arrhythmia primary prevention in patients with MS not only with the help of medicamentous AAT and MK but also other treatment methods. A decrease in the number of premature atrial contractions in MS patients cannot be considered a reliable criterion of the effectiveness of the disease primary prevention since in all MS patients both without AF and with the development of a disorder during therapy a significant decrease in the number of atrial ectopias was observed in comparison with the baseline data.

According to our data, modulated kinesotherapy, can be used in all patients with MS for AF primary prevention as it improves the structural and functional characteristics of the heart, reduces BMI, and the class of chronic heart failure; in addition, the method is harmless, and the positive result of the use is comparable to medicamentous AAT. In the future it is probably possible to use a combination of medicamentous AAT and MK as AF primary prevention in MS patients which is the subject of the further study.

## Conflict of Interest

A.I. Olesin declares no conflict of interest. I.V. Konstantinova declares no conflict of interest.

## Financing

The authors declare no funding for the study.

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**Author Contribution Statement**

*OAI* – data analysis, manuscript writing, approval of the final version, fully responsible for the content

*KIV* – data collection and analysis, editing, approval of the final version, fully responsible for the content

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***To cite:*** *Olesin A.I., Konstantinova I.V. The possibility of using pharmacological antiarrhythmic therapy and modulated kinesotherapy as a primary prevention of atrial fibrillation in patients with metabolic syndrome and with premature atrial complexes: prospective study. Complex Issues of Cardiovascular Diseases. 2022;11(1): 17-25. DOI: 10.17802/2306-1278-2022-11-1-17-25*