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# The use of antiarrhythmic drug treatment
## and modulated kinesitherapy for primary prevention of atrial fibrillation in patients with metabolic syndrome

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## Abstract

**Objective.** *To assess the effectiveness antiarrhythmic drug treatment (ADT) and modulated kinesitherapy (MK) for primary prevention of atrial fibrillation (AF) in patients with metabolic syndrome (MS) and premature atrial contractions (PACs).*

**Materials and methods.** *The study included 426 patients with MS and PACs aged from 58 to 72 years (average age — 66.4±0.7 years) with high risk of primary AF development (during one-year follow-up after the inclusion into the study). ADT with I–III antiarrhythmic agents was used for the primary AF prevention (excluding amiodarone) in 149 (34.97%) patients, MK — in 121 (28.40%), and blood pressure (BP), blood glucose and lipids level correction — in the rest. The primary endpoint after one-year follow-up was: the maintenance of sinus rhythm or AF registration.*

**Results.** *The rate of paroxysmal and persistent AF in patients prescribed with ADT and MK for the primary prevention of AF with MS and premature atrial contractions within one year after the first examination was 26.45% and 31.54%, respectively. The use of ADT and MK in patients with MS reduced the frequency of AF by 3 times on average compared with the correction of potentially modifiable MS risk factors.*

**Conclusion.** *The implementation of ADT with I–III antiarrhythmic agents as well as MK for the AF primary prevention in patients with MK with PACs and the risk of AF development one year after the first examination allowed to reduce the frequency of this arrythmia by 3 times compared with regular BP, blood glucose and lipids level correction.*

**Keywords:** *metabolic syndrome, primary atrial fibrillation prevention, antiarrhythmic therapy, modulated kinesitherapy.*

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## Introduction

Atrial fibrillation (AF) once developed in patients with metabolic syndrome (MS) usually recurs and transforms into permanent type [1]. Therefore, the primary prophylaxis of this arrhythmia in patients with MS is the basis for its prevention [1]. The primary prevention of AF includes the management of potentially modifiable MS risk factors, as well as the predictors for its development, such as premature atrial contractions (PACs) [1, 2]. Various types of physical activity are usually used for the management of MS [1, 2]. Modulated kinesitherapy (MK) is an aerobic exercise when patient walk in accordance with the heart rhythm [3]. Patients with MS with PACs and prognostic index for the development of AF ≤ 1.5, have high risk of AF development during 1 year follow-up [4]. It can be assumed that the increase of the prognostic index for the development of AF compared with baseline, for example, after MK and antiarrhythmic drug therapy (ADT) or other treatment in patients with MS, can be used as the criterion for the primary AF prevention effectiveness before the onset of clinical result. However, we have not found literature the data on the use of ADT and MK for AF primary prevention in patients with MS and PACs with high risk of AF.

The aim of the study was to assess the effectiveness of ADT and MK for primary prevention of AF in patients with MS and PACs.

## Materials and methods

The study included 426 patients with MS aged from 58 to 72 years (average age — 66.4±0.7 years). All the participants had the risk of AF development during 1-year follow up. The number of men and women was 186 (43.66%) and 240 (56.34%), respectively (p>0.05). MS was diagnosed according to generally accepted criteria [1].

After the clinical and instrumental examination that included echocardiography, daily electrocardiogram (ECG) monitoring, signal-averaged ECG registration, etc., the study inclusion criteria were determined among patients with MS. Instrumental methods for the determination of the left ventricular (LV) contractility and dysfunction, cardiac chambers volume, as well as the prognostic index for the development of AF, functional class of heart failure (assessed with 6-minute walk test), mean arterial blood pressure (BP) were described in details in previously published articles [4]. The prognostic index for AF development was calculated by the following formula: $(A \div B) \times (C \div N)$, where A and B are filtered "P" wave duration and dispersion determined by the data

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of signal-averaged atrial ECG and daily ECG monitoring, respectively (m/s), C — linear deviation of the corrected coupling interval of PACs, N — the number of PACs used for the study, expressed as number/hour [4]. At least 20 PACs were analyzed by the the corrected pre-ectopic interval in order to eliminate false positive results when determining the prognostic index of AF development [4]. The prognostic index for the development of AF ⩽ 1.5 in patients with MS with PACs predicted the occurrence of AF arrhythmia within one year after the examination [4]. It should be noted that the detection of PACs showed potential risk of primary AF development in patients with MS, however, the number of PACs per day or hour of observation did not affect the risk of AF [1, 2].

The CHARGE-AF risk score was used to determine the risk of AF development in dynamics by the following formula:

$$R_{CHARGE-AF} =$$
$$= 1 - 0.9718412736^{\exp[(\Sigma[K_1, K_2, K_3, K_4, K_5, K_6, K_7, K_8, K_9, K_{10}, K_{11}]) - 12.5815600]},$$

where

$R_{CHARGE-AF}$ — the risk of AF development by the CHARGE-AF risk score (in units),
K1 — (age in years ÷5)×0.5083;
K2 — ethnicity (caucasian/white: 1×0.46491);
K3 — (height in cm÷10)×0.2478;
K4 — (body mass in kg ÷15)×0.1155;
K5 — (systolic BP in mmHg.÷20)×0.1972,
K6 — (diastolic BP in mmHg ÷10)×0.1013,
K7 — current smoking (1×0.35931),
K8 — antihypertensive therapy (1×0.34889),
K9 — diabetes mellitus (1×0.23666),
K10 — chronic heart failure (functional classes from I to IV×0.70127);
K11 — history of myocardial infarction (1×0.49659). High risk of AF development was determined with RCHARGE-AF values over 0.76 [5].

The inclusion criteria were: the presence of sinus rhythm, subjective sensation of PACs, class I-II, of chronic heart failure according to NYHA, the absence of AF registration during at least 4–5 procedures of 1–3-day ECG monitoring at least once in 1–2 weeks for 2–3 months, left ventricular ejection fraction (LV EF) ⩾ 54% [4], prognostic index for the development of AF ⩽ 1.5, written informed consent for the participation in the study from the patient [4].

Patients with cardiomyopathies, heart valve disease and other pathologies presented in previously published articles [4] were excluded from the study.

AH was registered in 358 (84.04%) patients, diabetes mellitus — in 297 (69.72%), chronic obstructive pulmonary disease — in 96 (22.54%).

All study participants underwent BP correction with antihypertensive therapy, such as: indapamide, telmisartan, valsartan, etc. In order to improve the levels glucose and blood lipids, in addition to healthy diet, hypoglycemic and lipid-lowering medications were prescribed. The correction of potentially modifiable MS risk factors was considered as basic treatment.

At first, all patients, along with the basic treatment, underwent ADT. In case when patient refused to use pharmacological treatment, had side effects or contraindications, MK was prescribed. In case when patient had negative reaction to the use of ADT or MK, only basic treatment was performed. These patients were included into the control group.

All the participants initially received class II antiarrhythmic drugs, and class I or III drugs when the first-line treatment had no effect, such as: metoprolol, propranolol, carvediol, allapinin, ethacizine, propafenone, sotalol in average therapeutic doses, excluding amiodarone that is used for myocardial contractile dysfunction [2]. At baseline and after ADT that was carried out from 3–4 to 7 days, the prognostic index for the development of AF was determined: the increase of the prognostic index for the development of AF compared with baseline was considered as positive effect [4].

MK included walking in accordance with the heart rate [3, 6]. At first, MK was performed 2 times a day or more for 30–60 minutes for 5–7 days [5]. When positive effect was reached that was determined by the increase of prognostic index for the development of AF compared with baseline [6] MK was performed for at least 150 min/day [3, 6].

The development of AF during one-year follow-up was the endpoint of the study. In case when AF developed, anticoagulants such as dabigatran and rivaroxaban were prescribed [1, 2]. All the investigations were performed during sinus rhythm at least once every 1–2 months. When AF (paroxysmal or persistent) was determined, the investigations were performed after the management of AF, and pharmacological cardioversion was applied after 5-7 half-lives

of antiarrhythmic drugs that were used to eliminate this arrhythmia.

The results of statistical analysis are presented as mean values and standard error (M±m), standard deviation (σ), 95% confidence interval of the mean values, Student's t-test, chi-square test. The statistical significance was set as p<0.05. The Kolmogorov–Smirnov test and the ±3σ rule (gaussian distribution) was used to assess the normality of distribution. The comparison of two binary variables was performed using multiple logistic regression with the assessment of the odds ratio (OR) and standard error (SE) using the "Statistica" software, version 11.0.

## Study results

149 (34.97%) patients received ADT (ADT group), 121 (28.40%) — MK (MK group), the rest of the participants made up the control group. Groups did not differ significantly by gender, age, comorbid diseases, the results of clinical, laboratory and instrumental investigations.

Propranolol was the most effective medication in 33 (22.15%) patients from the ADT group, metoprolol — in 47 (31.54%), carvediol — in 26 (17.45%), ethacizine — in 15 (10.07%), allapinin — in 10 (6.71%), propafenone — in 8 (5.37%), sotalol — in the rest.

The studied parameters did not differ significantly between ADT and MK groups (Table 1).

During 1-year follow-up, paroxysmal and persistent types of AF were recorded in 32 (26.45%), 47 (31.54%) and 149 (95.51%) patients from ADT, MK and control group, respectively (p< 0.05), and the differences between the control and ADT and MK groups were statistically significant (Figure 1). The incidence of AF increased in patients over 65 years of age (OR = 8.93, SE = 0.94), with body mass index (BMI) > 35 kg/m$^2$ (OR = 5.5, SE = 0.92), left atrial end-diastolic volume index (LAEDVI) ⩾ 37 ml/m$^2$ (OR = 5.8, SE = 0.92), the ratio of the maximum early (E) to late (A) ventricular filling velocities (E /A) < 0.8 (OR = 2.5, SE = 1.3), prognostic index for the AF development < 0.5 units (OR = 12.8, SE = 1.6).

One year after the baseline, patients from the control group showed statistically significant decrease of the LV EF, E/A ratio, prognostic index for the development of AF parameters and 6-minute walk test, and the increase of LAEDVI, the number of PACs/hour, mean BP, BMI, RCHARGE-AF compared with baseline (table). The prognostic index for the development of AF statistically significantly increased and the number of PACs decreased in the ADT group, in the MK group — LV EF, the E/A ratio, the prognostic index for the development of AF, the results of the

Table 1. **Clinical and instrumental parameters, prognostic index for AF development, RCHARGE-AF in patients from ADT and MK groups at baseline (A) and one year after treatment (B)[1]**
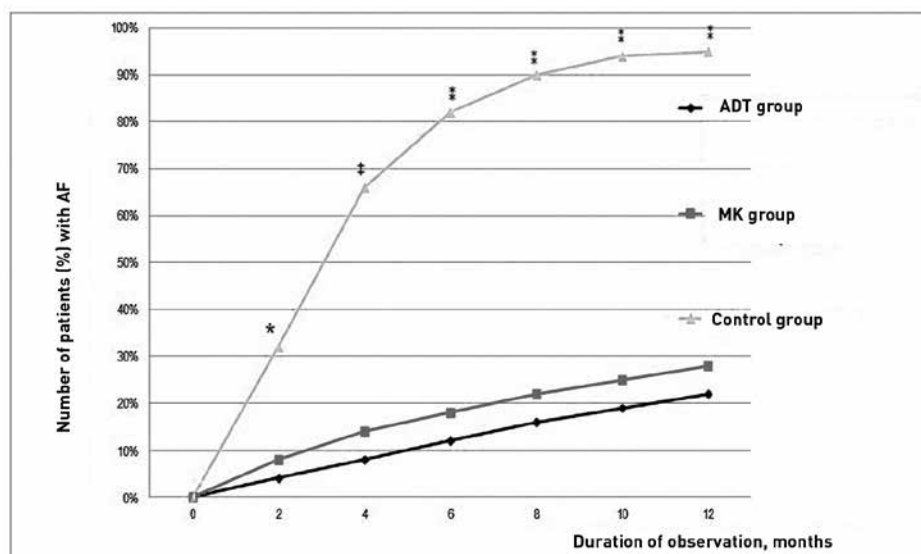
| Study group | Control group n=156 | | ADT group n=149 | | MK group n=121 | |
|---|---|---|---|---|---|---|
| Parameters | A | B | A | B | A | B |
| LV EF, % | 61.84±0.57 (54–69) | 54.01±0.66† (46–62) | 61.54±0.52 (55–68) | 60.38±0.65 (52–70) | 61.47±0.61 (54–68) | 68.35±0.81‡ (59–77) |
| E/A, units | 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/m$^2$ | 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) |
| PERs, 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) |
| PACs/hour | 172±6 (103–241) | 398±22† (126–687) | 182±7 (109–256) | 36±3* (8–64) | 180±7 (98–263) | 33±2* (9–58) |
| Mean BP, 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-walk test | 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) |
| RCHARGE-AF, units. | 0.82±0.02 (0.79–0.91) | 0.86±0.01† (0.81–0.93) | 0.84±0.02 (0.78–0.93) | 0.82±0.02 (0.75–0.87) | 0.84±0.02 (0.79–0.93) | 0.71±0.02‡ (0.67–0.78) |

**Comment.** PERs — positron-emitting radiopharmaceuticals; 1 — M±m (top of the table); 95 % confidence interval (bottom of the table).
*— statistically significant difference compared with the control group with p < 0,001,
† — compared with baseline with p < 0,05,
‡ — with p < 0,01.

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**Figure 1.** Cumulative proportion of patients ( %) with the development of AF in ADT and MK  groups.
**Comment.**  * — statistically significant difference between ADT and the control group with p < 0,05, ‡ — with p < 0,01, ⁑ —  with p < 0,001,
† — compared with MK group with p < 0,05.

6-minute test statistically significantly increased, and the LAEDVI, the number of PACs, mean BP, BMI, RCHARGE-AF — decreased compared with baseline. The rest of the parameters did not differ significantly (see table). The positive effect of the ADT and MK as primary prevention for AF in patients with MK was associated with the increase of the prognostic index for the development of AF by over 1.5 units (OR = 12.1, SE = 0.94), the decrease of RCHARGE-AF values compared with baseline (OR = 7.1, SE = 0.92) and, to lesser extent, with the decrease of the number of PACs per day (OR = 0.89, SE = 1.1).

## Discussion

The assessment of pulse rate according to the "pulse screening" principle that includes pulse palpation and its assessment with automatic or semi-automatic tonometers, followed by ECG recording by smartphone or by at the hospital is recommended for early diagnosis of AF in all patients, especially from older age group [7]. In recent years, patients with MS have been included into high-risk group for the development of AF. In case when their CHA2DS2VASc score of thromboembolic complications was ⩾ 1 and ⩾ 2 in men and women, respectively, — it is recommended to assess pulse rate daily and the increase of this score is associated with higher frequency of AF development [8, 9].

The study included 426 patients with MS aged from 58 to 72 years (average age — 66.4±0.7 years). The inclusion criteria were: sinus rhythm, the absence of AF registration, determined by at least 4–5 procedures of 1–3-day ECG monitoring at least once every 1–2 weeks for 2–3 months, the detection of PACs, the prognostic index for the development of AF ⩽ 1.5 that characterize the risk of AF development within one year after the inclusion into the study, and the presence of patient's written informed consent . The study endpoints were the maintenance of sinus rhythm or the development of AF.

Over the past years over 21 risk stratifications have been proposed, including the Framingham risk scales (1994–2019), in order to assesses the risk of AF development [10]. The meta-analysis of several risk stratifications (retrospective study) showed that the most informative model for 5-year prediction of AF onset of was the CHARGE-AF risk score [10] that include simple and available parameters, such as age, gender, anthropometric parameters, blood pressure, etc. [5]. The accuracy of RCHARGE-AF of 0.70–0.72 units by the CHARGE-AF risk score for primary AF prediction according to retrospective analysis of over 110.000 patients aged over 40 years old, is about 50%, and of 0.90 units — 90% [10, 11]. It should be noted that almost all patients with MS, especially those aged over 60 years old, who were assessed with CHARGE-AF score, had high or very high risk of AF development [5, 11].

Similar results were obtained in our study.

Currently, the mechanisms of AF development in patients with MS are not enough understood [1]. In

recent years, one the main hypothesis for AF development in this category of patients was the induction of AF by atrial cardiomyocytes overload with Ca++ ions during diastole caused by "oxidative stress" [1] that leads to atrial ectopic activity due to activation of trigger mechanisms and/or re-entry at the posterior wall of the left atrium that causes AF followed by its recurrence and/or preservation and transformation into permanent type [1]. It should be noted that the development of ectopic focus in the atria and/or pulmonary veins is quite rarely seen in patients with MS and AF [1, 2].

In most cases, PACs in patients with MS is interpreted as ectopia with potentially favorable prognosis that often does not require ADT, unless there is a subjective sensation of extrasystole that patient complain about [1, 2]. On the other hand, persistent and/or recurrent supraventricular ectopic activity can independently or indirectly disrupt cardiac conduction in the atria in this category of patients [1, 2]. However, the number of PACs per day is not associated with the risk of AF development in patients with MS [1, 2, 4].

In our study the risk of AF development was assessed by the prognostic index for the development of AF — the value of <1.5 units indicate the risk of AF registration within one year of observation [4].

To determine the prognostic index for the development of AF, we used signal-averaged atrial ECG data, P-wave dispersion, and the analysis of PACs preectopic interval [4]. The risk of AF development in patients with MS significantly increased with age, BMI, and its accuracy, in case of the decrease of this index in dynamics compared with baseline (<1.5 units), reached about 90% [4] .

The results of this study are consistent with previously obtained data.

The rate of AF registration was 26.45% and 31.54% in patients with MS who were administered with ADT and MK additionally to basic treatment for the primary prevention of AF, respectively (p>0.05). Positive effect of these methods for the primary prevention of AF in patients with MS highly correlated with the increase of the prognostic index for the development of this arrhythmia by > 1.5 units. Therefore, apparently, the increase of the prognostic index for the development of AF compared with baseline is a potential "preclinical" criterion that reflects the effectiveness of primary prevention of this arrhythmia in patients with MS, not only with ADT and MK, but also using

other treatment. It should be noted that all patients with MS, both without and with the development of AF, showed significant decrease in the number of PACs compared with baseline (OR between positive result of AF primary prevention and the decrease of PACs frequency did not exceed 0.89), after ADT and MK treatment. Therefore, the decrease in the number PACs not only after ADT and MK, but also after other treatment in patients with MS, cannot be a reliable criterion to assess the effectiveness of ongoing primary AF prevention.

Positive effect of ADT in patients with MS seem to be mainly associated with the elimination of electrophysiological mechanisms for the development of PACs [2], since there was no significant change of hemodynamic parameters, class of chronic heart failure, BMI, RCHARGE-AF in ADT group after treatment.

The data on the use of antiarrhythmic drugs in patients with MS and atrial ectopic activity for the primary prevention of AF are scarce that can be associated with increased risk of adverse events compared with positive result [1, 2]. ADT for the primary prevention of AF in patients with MS with PACs, is mostly used in patients with high and very high risk of AF development, from several months to a year, in particular [2]. On the other hand, the absence of dynamics in the risk of AF development in patients with MS, according to the data obtained, which was determined by the CHARGE-AF risk score, despite the use of ADT, highlights the importance of the correction of potentially modifiable risk factors, such as obesity, smoking , etc., along with ADT [1, 2].

All patients with MS, along with a positive result of MK that was used as for the primary prevention of AF, showed the decrease of cardiac chamber size, LV dysfunction, BMI and RCHARGE-AF values.

The positive effect of MK in patients with MS can be explained by the decrease of cardiac afterload, LV dysfunction and left atrial volume, as consequence of the reduction of circulating blood volume due to the decrease of BMI, epicardial adipose tissue, and vasodilation [1, 2 , 3, 12], as well as due to the accumulation of stress-protective proteins, the increase of prostaglandin activity, which limit the activation of sympathetic-adrenergic system, increase the resistance of cardiomyocytes to the damaging effect of "oxidative stress" and eliminate the "arrhythmogenic substrate" for the development of AF [1, 2, 12].

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The use of the combination of ADT and MK for the primary prevention of AF in patients with MS will be the subject for further investigation.

## Conclusion

The use of ADT and MK for the primary prevention of AF in patients with MS and the risk of AF development within one year after examination, allowed to reduce the frequency of its development by 3 times compared with the correction of potentially modifiable risk factors such as BP, blood glucose and lipid level. MK can be recommended for all the patients with MS, since it improves structural and functional cardiac characteristics, reduce BMI, class of chronic heart failure and the risk of AF development. This methods has no adverse effects and its effectiveness in the prophylaxis of AF is comparable to ADT. The increase of the prognostic index for the development of AF in dynamics compared with baseline and its value over 1.5 units can become a potential «preclinical» criterion that reflects the effectiveness of primary prevention of this arrhythmia not only with ADT and MK, but also using other treatment strategies.

**Conflict of interest:** none declared.

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