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Research article



Correction of Potentially Modifiable Components of Metabolic Syndrome for the Primary Prevention of Atrial Fibrillation in Comorbid Patients with Premature Atrial Complexes

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AIM: The study aimed to evaluate the influence of the correction of potentially modifiable risk factors for the development of atrial fibrillation (AF) as primary prevention of AF in patients with metabolic syndrome (MS) and premature atrial complexes (PAC).

MATERIALS AND METHODS: We monitored 856 MS patients with PAC, aged 58–72 (mean age, 66.4 ± 0.7) years, in the north-western region of the Russian Federation. A 5-year risk of AF was calculated in all patients after the examination by determining the potential prognostic time range for Af development and its index of probable occurrence ($R_{\text{CHARGE-AF}}$) using the CHARGE-AF model. The correction of potentially modifiable MS components and risk factors for AF development (smoking cessation, elimination of physical inactivity, etc.) until their target values were achieved was offered to all patients. The follow-up endpoint was the preservation of sinus rhythm or AF registration.

RESULTS: All patients with MS were distributed into three groups. Group I consisted of 557 (65.07%) patients with incomplete correction of risk factors, and group II included 93 (10.86%) who achieved the target values of all potentially modifiable factors for AF development. The control group included the remaining patients without quantitative and qualitative changes in the dynamics AF predictors. No significant differences were found between the groups in terms of sex, age, concomitant diseases, and risk factors for AF. The achievement of the target values of the main MS components, including body mass index and/or waist circumference, correlated with the performance of regular aerobic exercises (odds ratio [OR] = 8.9), adherence to a diet (OR = 7.5), duration of MS diagnosis < 20 years before the start of correction (OR = 12.8), and intake of a glucagon-like peptide-1 receptor agonist (Liraglutide) (OR = 5.4).

In the control group, group I, and group II, AF development did not differ significantly and was registered in 192 (93.20%), 491 (88.15%), and 79 (84.95%) patients ($p > 0.05$), respectively.

CONCLUSIONS: In MS patients with PAC and a high 5-year risk of AF, the correction of potentially modifiable risk factors for AF development, as its primary prevention, is ineffective. The determination of the $R_{\text{CHARGE-AF}}$ index in MS patients with PAC in dynamics indicates the efficiency of the correction of potentially modifiable risk factors for AF development, but it does not determine the degree of the risk of its occurrence.

The authors declare no conflict of interest.

Keywords: primary prevention of atrial fibrillation; correction of potentially modifiable components of the metabolic syndrome.

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Научная статья

Роль коррекции потенциально модифицируемых компонентов метаболического синдрома для первичной профилактики фибрилляции предсердий у коморбидных больных с преждевременными предсердными комплексами

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Цель исследования — оценить влияние коррекции потенциально модифицируемых факторов риска развития фибрилляции предсердий (ФП) в качестве первичной профилактики этой аритмии у пациентов метаболическим синдромом (МС) с внеочередными предсердными комплексами (ВПК).

Материал и методы. Наблюдалось 856 больных МС с ВПК Северо-Западного региона РФ в возрасте от 58 до 72 лет (в среднем $66,4 \pm 0,7$ года). У всех пациентов после обследования был рассчитан пятилетний риск развития ФП путем определения потенциально-прогностического временного диапазона ее развития и индекса вероятного возникновения этой аритмии ($R_{\text{CHARGE-AF}}$), используя модель CHARGE-AF. Всем больным предлагалась коррекция потенциально модифицируемых компонентов МС и факторов риска развития ФП (отказ от табакокурения, устранение гиподинамии и т.д.) до достижения их целевых значений. Конечной точкой наблюдения считали сохранение синусового ритма или регистрация ФП.

Результаты. Все больные МС были распределены на три группы. I группу составили 557 (65,07 %) пациентов с неполной коррекцией, во II группу вошли 93 (10,86 %) — с достигнутыми целевыми значениями всех потенциально модифицируемых факторов формирования ФП. Остальные пациенты без количественного и качественного изменения в динамике наблюдения предикторов развития этой аритмии были включены в контрольную группу. По полу, возрасту, сопутствующим заболеваниям, факторам риска развития ФП достоверного различия между группами выявлено не было. Достижение целевых значений основных компонентов МС, включая индекс массы тела и/или окружность талии, коррелировало с выполнением регулярных аэробных физических нагрузок [отношение шансов (ОШ) = 8,9], соблюдением диеты (ОШ = 7,5), продолжительностью регистрации МС менее 20 лет до начала коррекции (ОШ = 12,8), использованием агониста рецептора глюкагоноподобного пептида-1 (лираглутида) (ОШ = 5,4).

В контрольной, I и II группах развитие ФП достоверно не различалось и наблюдалось у 192 (93,20 %), 491 (88,15 %) и 79 (84,95 %) пациентов ($p > 0,05$) соответственно.

Заключение. У больных МС с ВПК и высоким пятилетним риском развития ФП коррекция потенциально модифицируемых факторов риска развития ФП, используемая в качестве ее первичной профилактики, неэффективна. Определение индекса $R_{\text{CHARGE-AF}}$ у больных МС с ВПК в динамике отражает эффективность коррекции потенциально модифицируемых факторов риска развития ФП, но он не определяет степень риска ее развития.

Ключевые слова: первичная профилактика фибрилляции предсердий; коррекция потенциально модифицируемых компонентов метаболического синдрома.

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BACKGROUND

The combination of metabolic syndrome (MS) components, such as abdominal obesity, arterial hypertension, diabetes mellitus, and dyslipidemia, determines the potential cardiometabolic risk for the occurrence of various cardiovascular diseases, including atrial fibrillation (AF) [1–5]. The effect of the correction of potentially modifiable MS components has been studied quite well in patients with existing AF (paroxysmal and persistent), and in relation to the development of primary AF, retrospective assessments of the change in the risk of its occurrence, depending on the achievement of target values, such as the body mass index (BMI), have been conducted [1, 2, 5–8].

Hypothetically, the correction of potentially modifiable MS components and other risk factors for AF development in patients with premature atrial complexes (PAC) will result in a decrease in the primary occurrence of AF in high-risk cases. However, no prospective studies have investigated the correction of potentially modifiable risk factors for AF development as primary prevention of AF in MS patients with PAC.

This study aimed to evaluate the effect of the correction of potentially modifiable risk factors for AF development, as primary AF prevention, in MS patients with PAC.

MATERIALS AND METHODS

We monitored 856 MS patients with PAC, aged 58–72 (mean age, 66.4 ± 0.7) years, in the north-western region of the Russian Federation (St. Petersburg, Leningrad region, etc.). There were 398 (46.50%) men and 458 (55.50%) women ($p > 0.05$).

The criteria for inclusion in the study were determined in all patients after clinical, laboratory, and echocardiographic examinations, daily electrocardiogram (ECG), monitoring registration of a signal-averaged ECG, etc. The methods and instruments used for determining the contractility and dysfunction of the left ventricle, volume of cardiac chambers, duration of FiP-P, Pd, prognostic index (PI) for AF development by analyzing PAC, criteria for diagnosing MS, physical inactivity, heart failure grade (6-minute walk test), and mean arterial pressure (BP) are presented in previous studies [7, 9–11].

Based on the analysis of atrial ectopias, PI was calculated as follows: $PI = (A \div B) \times (C \div N)$, where A and B are the duration of FiP-P and Pd determined from signal-averaged atrial ECG data and 24-h ECG monitoring, respectively (ms), C is the linear deviation of the corrected coupling interval in more than 20 premature atrial contractions, and N is the number of extra supraventricular complexes used for the study, expressed as their number per hour [10, 11]. To avoid false-positive results of PI determination when calculating it, the corrected pre-ectopic interval of PAC was analyzed in at least 20 supraventricular ectopias [10, 11].

PI was used because the detection of atrial ectopia determines the potential risk of primary AF in patients with

MS given its uncertain implementation in time [3–5, 7]. The total number of extrasystoles, for example, per day of monitoring does not reflect the risk degree of this arrhythmia [3–5, 7].

The 5-year risk for AF was determined when the FiP-P was ≥ 135 ms with the FiP-P/Pd ratio of ≤ 2.5 units [9, 10], followed by PI assessment during follow-up and calculation of the potentially predictive time range for AF development (PTRAF) [12]. Before determining PTRAF, PI was recorded 2–3 times with an interval of 1–3 months. If the PI value decreased in comparison with the initial data, the PTRAF (months) was calculated according to the previously proposed equation [12] $PTRAF = [PI_1 - 0.01] \div [PI_1 - (PI_2, PI_3, \text{etc.})] \times I$, where PI_1 is the PI values after study 1; $PI_2, PI_3, \text{etc.}$, are values of PI_2, PI_3 , respectively, at studies 2, 3, and subsequent studies; 0.01 is the PI value at which spontaneous attacks of AF are registered [11, 12]; and I is the interval (months) between study 1 and subsequent (2–3, etc.) studies [12]. The accuracy of determining PTRAF was approximately 86% [10, 12].

The CHARGE-AF model [13] in patients followed up was used to determine the potential risk index for AF occurrence ($R_{\text{CHARGE-AF}}$) according to the following equation:

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

where $R_{\text{CHARGE-AF}}$ is the index of the potential risk of AF occurrence according to the CHARGE-AF system (units);

K_1 is the (age in years $\div 5$) $\times 0.5083$;

K_2 is ethnicity (Caucasian/White: 1×0.46491);

K_3 is the (height in centimeters $\div 10$) $\times 0.2478$;

K_4 is the (weight of the patient in kg $\div 15$) $\times 0.1155$;

K_5 is the (systolic BP in mm Hg $\div 20$) $\times 0.1972$;

K_6 is the (diastolic BP in mm Hg $\div 10$) $\times 0.1013$;

K_7 is current tobacco smoking (1×0.35931);

K_8 is the intake of antihypertensive drugs (1×0.34889);

K_9 is diabetes mellitus (1×0.2 to my knowledge, references 3666);

K_{10} is chronic heart failure (grades I–IV $\times 0.70127$);

K_{11} is history of myocardial infarction (1×0.49659) [13].

A high 5-year risk of AF was considered at $R_{\text{CHARGE-AF}}$ values of ≥ 0.72 units [13].

The inclusion criteria were as follow: sinus rhythm, detection of PAC ≥ 100 of supraventricular extrasystoles per day of monitoring [8, 10, 11], chronic heart failure of grades I–II according to the New York Heart Association, absence of AF registration during at least 4–5 procedures of 1–3-day ECG monitoring at least one time per 1–2 weeks for 2–3 months, preserved left ventricular ejection fraction (LVEF) $\geq 50\%$ [10, 11], determination of 5-year PTRAF using PI [12], values of $R_{\text{CHARGE-AF}}$ of ≥ 0.72 units [13], and informed consent to the examination and treatment [10, 11]. The exclusion criteria were as follows: myocarditis, cardiomyopathies, and other pathologies [10, 11].

Hypertension was diagnosed in 715 (83.53%) patients, diabetes mellitus in 528 (61.68%), chronic obstructive pulmonary disease in 196 (22.90%), a history of myocardial

infarction in 89 (10.40%), smoking in 524 (61.21%), and physical inactivity in 694 (81.07%).

The correction of MS components and other risk factors for AF was offered to all patients, such as smoking cessation, elimination of physical inactivity, etc. The target values for the correction of MS components included a decrease in BMI < 25 kg/m² and/or waist circumference of 80 cm and 94 cm or lower in women and men, respectively; BP of 130/80 mm Hg or lower; total cholesterol and triglyceride levels in the blood plasma of 5.2 mmol/L and 1.7 mmol/L or lower, respectively; plasma low-density lipoprotein cholesterol level of 3.0 mmol/L or lower; fasting blood glucose level of 5.8 mmol/L or lower; and increase in plasma high-density lipoprotein cholesterol level to 1.0 mmol/L or higher in men and to 1.2 mmol/L or higher in women [3–7, 14]. To correct MS components such as BMI and/or waist circumference, diet, regular aerobic exercises (lasting ≥ 150 min per week), and smoking cessation were recommended, whereas antihypertensive drugs (indapamide, telmisartan, valsartan, etc.) and hypoglycemic and hypolipidemic agents (diet, metformin, empagliflozin, liraglutide, statins, etc.) were used to normalize BP, glucose levels, and blood lipids [6–8, 14]. Antiarrhythmic therapy was not used to eliminate PAC.

The efficiency of the correction of potentially modifiable MS components and risk factors for AF development was evaluated (points) using the equation $K \times D$, where K is equal to “0” and “1” in the absence of correction and incomplete correction (not reaching the values of the “health passport” [6–8, 14], respectively, “2” is upon reaching the target values of the predictors of AF (units); and D is the duration of the corrected risk factors after their modification (months)).

Patients were followed up for 1–5 years. AF registration or maintenance of sinus rhythm was the endpoint of this study. Anticoagulants (dabigatran, rivaroxaban, etc.) were prescribed if AF occurs [1, 2]. All studies were conducted in sinus rhythm at least once every 1–2 months. The values of BMI, waist circumference, BP, and fasting blood glucose were recorded by medical staff. Patients performed daily pulse control independently at least two times a day, using, as a rule, automatic blood pressure monitors. If an irregular pulse was detected, an ECG was recorded on a smartphone or when visiting a family doctor’s office, polyclinic, etc. [1, 6, 7, 15–17]. When AF (paroxysmal or persistent) appeared, the studies were performed after the relief of the first attack, and in the case of pharmacological cardioversion, these were performed after 5–7 half-lives of the antiarrhythmic drugs used to eliminate AF.

For statistical processing of the data, the mean values and their error ($M \pm m$), mean-square deviation (σ), 95% confidence interval of the mean values, Student’s t -test, and χ^2 test were used, and $p < 0.05$ was taken as a significant difference in the indicators. The normality of distribution of the quantitative indicators was assessed using the Kolmogorov–Smirnov test, and according to the $\pm 3\sigma$ rule

(Gaussian distribution), Pearson’s linear pairwise correlation and Spearman’s rank correlation (for non-parametric indicators) (r) were used. Moreover, the comparison of two binary variables was evaluated by multivariate logistic regression with the determination of the odds ratio (OR). Statistica version 11.0 software was used.

The study was performed in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki.

RESULTS

After inclusion in the study, PTRAF ranged from 6 to 12 months in 284 (33.18%) patients with MS, from 1 to 3 years in 255 (29.79%) patients, and from 4 to 5 years in the rest of the patients. Depending on the main MS component (BMI and/or waist circumference) modification, all patients were distributed into three groups, where group I consisted of 557 (65.07%) patients with an incomplete correction (1 point), and group II included 93 (10.86%) patients with achieved target values (2 points) of BMI and/or waist circumference. The control group included the remaining patients without correction (0 points) or with incomplete correction (1 point) of these components for no more than 2–3 months.

Upon study enrollment, a significantly shorter duration of MS registration before the start of correction was revealed in group II than in group I and control group (Table 1). Significant differences in other studied parameters (Tables 1, 2), as well as in sex, age, frequency of detection of hypertension, diabetes mellitus, chronic obstructive pulmonary disease, myocardial infarction, smoking, and physical inactivity, were not revealed between groups I and II and when compared with the control group.

In groups I and II (in group II to a greater extent), a significant decrease in BMI and/or waist circumference was found when compared with the control group, and the efficiency of correction of other indicators in these groups was comparable, approaching the target indicators (Table 3). The achievement of target values of BMI and/or waist circumference correlated with regular aerobic exercise (OR = 10.9), adherence to a diet (OR = 8.5), duration of MS registration < 20 years before correction (OR = 12.8), and intake of a glucagon-like peptide-1 receptor agonist (Liraglutide) (OR = 5.4).

After the examination, recurrent AF (paroxysmal and persistent) was registered in 192 (93.20%), 491 (88.15%), and 79 (84.95%) patients of the control group, group I, and group II, respectively ($p > 0.05$) (Fig. 1). Lethal outcomes, myocardial infarction, stroke, or other complications did not occur during follow-up.

In the control group, by the end of the predicted period of AF development or when it occurred, a significant decrease in LVEF, E/A ratio, mean BP, 6-minute walk test distance, and $R_{\text{CHARGE-AF}}$ and a significant increase in PACs and end-diastolic volume of the left atrium (EDVLA) index were found.

In group I, only a significant decrease in mean BP and $R_{\text{CHARGE-AF}}$ was found, whereas other indicators in these groups did not change significantly when compared with initial data (Table 2). In group II, AF development was noted despite a significant decrease in $R_{\text{CHARGE-AF}}$, mean BP, EDVLA index, and PAC and a significant increase in LVEF, E/A, and 6-minute walk test

distance when compared with baseline data (Table 2). In all patients, the decrease in PI during follow-up was mainly due to a decrease in the variability of the PAC coupling interval (OR = 5.2), an increase in Pd (OR = 4.9) and, to a lesser extent, as a result of a change in the number of supraventricular extrasystoles (OR = 0.91).

Table 1. Clinical and instrumental indicators and PTRAF in groups I and II upon inclusion in the study¹

Indicators	Control group n = 206	Group I n = 557	Group II n = 93
Age, years	66.9 ± 0.63 (58.4–74.7)	65.9 ± 0.36 (61.8–73.9)	65.9 ± 0.8 (57.7–69.8)
BMI, kg/m ²	36.4 ± 0.48 (30.3–41.4)	36.1 ± 0.32 (30.1–42.1)	35.8 ± 0.42 (31.5–39.4)
WC, cm	129.2 ± 1.5 (108–147)	131.4 ± 1.1 (110–152)	130.2 ± 1.9 (105–148)
BG, mmol/L	9.4 ± 0.4 (6.4–14.7)	9.1 ± 0.25 (6.3–13.9)	8.8 ± 0.8 (6.8–14.9)
TC, mmol/L	7.9 ± 0.1 (6.2–9.6)	8.1 ± 0.1 (6.5–10.7)	8.2 ± 0.2 (6.4–9.9)
LDLC, mmol/L	4.6 ± 0.2 (3.6–5.8)	4.8 ± 0.1 (3.8–6.2)	4.1 ± 0.2* (3.2–5.6)
HDLC, mmol/L	1.0 ± 0.1 (0.7–1.4)	0.9 ± 0.1 (0.7–1.5)	1.1 ± 0.5 (0.8–1.4)
TG, mmol/L	2.5 ± 0.1 (1.5–3.4)	2.4 ± 0.1 (1.4–3.5)	2.6 ± 0.2 (1.7–4.4)
Duration of MS registration before correction, years	39.3 ± 0.8 (29–52)	38.7 ± 0.8 (27–54)	14.1 ± 1.1* (8–20)
Potential period of time for the onset of primary AF, months	34.6 ± 2.1 (4–59)	35.2 ± 1.3 (6–58)	36.9 ± 3.2 (5–60)

Note: ¹, above $M \pm m$; below, 95% confidence interval of mean values; * significant difference in indicators when compared with the control group, [†] group II compared with group I ($p < 0.05$). MS, metabolic syndrome; AF, atrial fibrillation; PTRAF, potentially predictive time range for AF development; BMI, body mass index; WC, waist circumference; BG, blood glucose; TC, total cholesterol; LDLC and HDLC, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, respectively; TG, triglycerides.

Table 2. Clinical and instrumental indicators and $R_{\text{CHARGE-AF}}$ in groups I and II upon inclusion in the study (A) and by the end of the predicted period of AF development or when it occurs (B)¹

Patient groups	Control group n = 206		Group I n = 557		Group II n = 93	
	A	B	A	B	A	B
LVEF, %	61.84 ± 0.67 (54–69)	54.01 ± 0.68 [†] (46–62)	61.54 ± 0.32 (55–68)	60.38 ± 0.35 (52–70)	61.47 ± 0.89 (54–68)	68.35 ± 0.91 [†] (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)
EDVLA index, 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)	31.53 ± 0.43 [†] (27–38)
Number of PAC per hour	372 ± 6 (303–441)	598 ± 22 [†] (326–887)	382 ± 3 (309–456)	371 ± 8 (189–564)	389 ± 11 (298–463)	342 ± 16 [†] (259–418)
Average BP, mm Hg	117.1 ± 1.2 (103–131)	108.7 ± 0.9 [†] (97–121)	118.1 ± 0.7 (102–132)	107.8 ± 0.5 [†] (96–119)	118.9 ± 1.4 (104–131)	105.2 ± 1.3 [†] (95–116)
6-minute walk 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)
$R_{\text{CHARGE-AF}}$ units	0.82 ± 0.02 (0.73–0.91)	0.86 ± 0.01 [†] (0.76–0.94)	0.81 ± 0.01 (0.74–0.92)	0.69 ± 0.01 [†] (0.62–0.78)	0.83 ± 0.01 (0.79–0.92)	0.48 ± 0.01 [†] (0.43–0.56)

Note: ¹, above $M \pm m$; below, 95% confidence interval of mean values, * significant differences in indicators when compared with the control group at $p < 0.05$, [†] initial data ($p < 0.05$). AF, atrial fibrillation; LVEF, left ventricular ejection fraction; E/A, ratio of the maximum blood flow rates through the mitral valve during left ventricular diastole (E) and atrial systole (A); EDVLA, end-diastolic volume of the left atrium; PAC, premature atrial complexes; BP, blood pressure; $R_{\text{CHARGE-AF}}$, prognostic index for AF development according to CHARGE-AF risk stratification.

Table 3. Efficiency of the correction of potentially modifiable components and predictors of AF development in groups I and II (points)¹

Indicators	Control group n = 206	Group I n = 557	Group II n = 93
BMI	0.23 ± 0.21 (0–3)	22.15 ± 0.52* (12–34)	38.84 ± 3.02* [♦] (12–70)
WC	0.21 ± 0.19 (0–3)	16.4 ± 0.21* (12–25)	39.2 ± 3.04* [♦] (112–70)
BG	0.12 ± 0.17 (0–2)	37.24 ± 1.38* (12–72)	35.32 ± 3.67* (12–68)
TC	0.11 ± 0.14 (0–2)	29.43 ± 1.46* (12–52)	32.48 ± 3.37* (12–56)
Smoking cessation	0.21 ± 0.16 (0–3)	25.16 ± 0.96* (12–46)	26.84 ± 1.87* (12–45)
Arterial pressure	0.22 ± 0.19 (0–3)	36.45 ± 1.35* (12–69)	37.32 ± 3.74* (10–67)
Aerobic exercise	0.12 ± 0.12 (0–2)	25.27 ± 0.42* (11–43)	41.17 ± 3.34* [♦] (11–70)
LDLC	0.12 ± 0.11 (0–2)	31.67 ± 1.24* (10–54)	33.87 ± 3.46* (12–58)
HDLC	0.22 ± 0.16 (0–3)	23.76 ± 0.75* (12–39)	24.96 ± 1.65* (12–38)
TG	0.19 ± 0.15 (0–3)	35.28 ± 1.38* (12–68)	36.73 ± 3.34* (12–66)

Note: The designations are the same as in Table 1.

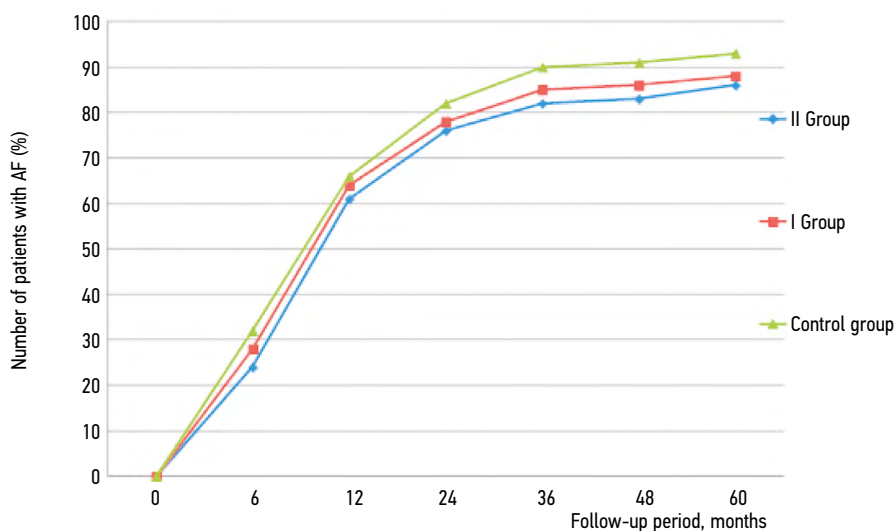


Fig. 1. Cumulative proportion of patients with AF (%) in groups I and II. * — significant difference in indicators when compared with the control group ($p < 0.05$). AF, atrial fibrillation.

DISCUSSION

For the early diagnosis of AF in all patients with MS, especially in the older age group with risk factors for AF development including those at risk of thromboembolic complications, particularly according to the CHA₂DS₂-VASc scale, a daily assessment of pulse regularity according to the “pulse screening test” principle, determined by both palpation and use of household blood pressure monitors, followed, if necessary, by ECG registration on a smartphone or when visiting a medical institution, is recommended [1, 6, 7, 15–17].

To assess the risk of the first episodes of AF, including in patients with MS, along with the Framingham scales (1994–2019), at least 21 risk stratifications were proposed [18]. A meta-analysis of risk stratifications showed that the CHARGE-AF system was found to be the most informative 5-year model for predicting AF development [19], including indicators such as age, anthropometric parameters, ethnicity, BP level, etc. [13, 19]. According to a retrospective analysis of more than 110,000 patients aged > 40 years, the accuracy of the primary prediction of AF using the CHARGE-AF model in detecting the R_{CHARGE-AF} values in the range of 0.70–0.72 units

averaged about 50%, and with values of this indicator of about 0.80 units, the prognostic significance increased to 70% [13, 19]. In the majority of patients with MS in the older age group, the probability of AF was high when CHARGE-AF risk stratification was used [13, 19]. In patients with MS, there is an obesity paradox or metabolic paradox, in which patients who are obese have a minimal probability of lethal outcomes from various cardiovascular diseases and their complications [2–7].

Similar data were obtained in the present study.

The study of the mechanisms of AF development in patients with MS remains one of the urgent problems of arrhythmology and is the subject of ongoing study based, in most cases, on experimental data [2, 6, 7, 20]. Currently, in these patients, the theory of AF induction resulting from Ca^{++} ion overload in atrial cardiomyocytes during diastole due to oxidative stress is widespread, including inflammation of the epicardial adipose tissue [20]. These events result in atrial ectopia caused by the activation of trigger mechanisms and/or re-entry, specifically in the posteroinferior wall of the left atrium, leading initially to the formation of a “rotor” in this zone. Consequently, AF developed with its subsequent recurrence and/or preservation as a permanent type [6, 7, 20]. In patients with MS and AF, ectopic foci in the pulmonary veins and/or atria are rarely detected, and their detection is usually accidental [2, 5–8].

In the present study, in patients with MS, PI was determined based on the assessment of the R-R sinus rhythm-corrected coupling interval of PAC, their number, FiP-P, and Pd [10, 11]. Based on the analysis of PI during follow-up, PTRAF (months) was determined, presented as the original equation

$$PTRAF = [PI_1 - 0.01] \div [PI_1 - (PI_2, PI_3, \text{etc.})] \times I,$$

where PI_1 is the value after study 1; $PI_2, PI_3, \text{etc.}$, are PI values at studies 2–3 and subsequent studies, respectively; 0.01 is the PI value at which spontaneous AF attacks occur [11]; and I is the interval (months) between study 1 and subsequent (2–3, etc.) studies [12].

After inclusion in the study, PTRAF ranged from 6 to 12 months in 33.18% of patients with MS, from 1 to 3 years in 29.79% of patients, and from 4 to 5 years in the remaining patients.

Currently, the primary prevention for cardiovascular diseases is determined by four main health factors, namely, normal BP values ($BP \leq 129/84$ mm Hg), BMI (19–25 kg/m^2), lipids, and blood glucose, and three behavioral factors, namely, cessation of bad habits (smoking, drinking alcohol, etc.), regular aerobic exercises, and adherence to a diet, mainly Mediterranean diet [6–8, 14]. It can hypothetically be assumed that the achievement of the target values of MS components related to health factors may be the basis for the primary prevention of AF in these patients. With the use of modern drug therapy in the vast majority of patients with MS, generally, the target values of BP, cholesterol, and blood glucose levels are achieved, whereas the normalization of

BMI and/or waist circumference requires targeted induction or ingenuous sincere desire of the patient, for example, by self-monitoring with weekly recording of these parameters and their registration in case diary [3–8, 14]. Even if the ideal body weight is achieved, it does not necessarily mean that it will be maintained for an indefinitely long time [3, 4, 14].

Therefore, in this study, the efficiency of the correction of potentially modifiable MS components and predictors of AF development were determined (in points) taking into account cases of absent correction (0) or incomplete correction (1), achievement of target values of potentially modifiable AF predictors (2), and duration of the maintenance of the modifiable factors achieved (months). The main components of MS, used as a basis in the analysis of the correction efficiency, were BMI and waist circumference [3, 4, 6–8, 24]. In this study, 65.07% of the patients had incomplete correction of BMI and waist circumference, and 10.86% of the patients achieved the target values of all MS components and risk factors for AF. In 24.07% of the patients, despite the recommendations for the implementation of a healthy lifestyle, almost no correction of all predictors of AF was registered. In patients with incomplete reversal of BMI and/or waist circumference to the target values, other risk factors for AF development (levels of BP, lipids, and blood glucose, smoking cessation, etc.) approached the values corresponding to apparently healthy individuals, maintained as usual for at least 6 months. The achievement of the target values of the main components of MS, including BMI and/or waist circumference, correlated with the performance of regular aerobic exercises (OR = 10.9), adherence to a diet (OR = 8.5), duration of MS registration < 20 years before the start of correction (OR = 12.8), and intake of a glucagon-like peptide-1 receptor agonist (Liraglutide) (OR = 5.4).

In the overwhelming majority of cases, the effect of the correction of potentially modifiable MS components and predictors of AF is assessed retrospectively to determine a change in the risk (%) of AF development. In the REGARDS study, the significance of correction of each MS component and behavioral factors that reached the target values in relation to reducing the AF risk, depending on the degree of correction of potentially modifiable factors, was 5%–10% [24], whereas in the ARIC study, it was 12%–17% [8], and the normalization of BP and body weight play the leading role in reducing the risk of AF [8, 24, 25, 26]. The heterogeneity in the significance of the correction of each AF predictor was attributed to the use of different assessment methods. In another review that focused on primary AF prevention through the correction of potentially modifiable factors, the reduction in AF risk was approximately 18% with the normalization of BP and BMI, up to 10% with regular aerobic exercises, up to 10% with smoking cessation, and 2.5% and 5% with the normalization of lipid and blood glucose levels, respectively [25]. In summary, it can be assumed that the total correction of all MS components and behavioral factors, except for BMI and/or waist circumference, can hypothetically reduce the risk

of AF by approximately 40% and by 60% when the latter two parameters are included. Based on the proposed reduction in the risk of primary AF due to the correction of potentially modifiable predictors of its development, it can be hypothetically assumed that in the prospective monitoring of patients with a high cardiometabolic risk, at least a twofold decrease in the occurrence of AF can be expected, compared with patients with abdominal obesity and other components of MS.

The study results showed that in patients, upon reaching the target values, without correction and with incomplete correction of all MS components and risk factors for AF development, the incidence of primary AF attacks did not differ significantly, as it was recorded in 84.95%, 93.20%, and 88.15% of the cases, respectively.

In most cases, PAC in patients with MS is regarded as supraventricular ectopia with a favorable prognosis, usually not requiring antiarrhythmic drugs, except for the presence of a subjective sensation of extrasystole [1–3]. On the contrary, in these patients, sustained and/or recurrent supraventricular ectopia with a coupling interval, for example, of ≤ 600 ms with low variability (< 60 ms) may, alone or indirectly, along with an increase in calcium current to atrial myocytes, be activated simultaneously, rectifying input potassium flows, thereby initially inducing myocardial regions with heterogeneous refractoriness, followed by electrical and structural remodeling of the left heart, causing particularly atrial arrhythmogenic cardiomyopathy and subsequently AF [2, 5–7, 20–22]. This fact is indirectly confirmed by the results of our study, that is, a decrease in PI values due to a reduction in the variability of the PAC coupling interval, an increase in Pd, and, to a lesser extent, a change in the number of extrasystoles, which, apparently, reflects the process of formation of the substrates for AF development [21, 23].

Thus, the complex correction of potentially modifiable predictors of AF development, reaching target values, as primary prevention of AF in MS patients with PAC, when a high risk of its development is detected, is ineffective. One of the reasons for the lack of influence of the modification of MS components, including reaching the target values, on the course of PAC and primary AF development, is the registration of atrial ectopia indefinitely before study inclusion, inducing the occurrence of atrial myocardial zones

with the dispersion of conduction and refractoriness and/or the formation of multiple ectopic foci [5–7], and the rather slow regression of the excess volume of epicardial adipose tissue in patients with MS [1–4]. Therefore, frequent and persistent atrial premature beats in comorbid patients with abdominal obesity, apparently, is one of the independent predictors of AF development, determining independently or indirectly the high risk of its development [7, 8, 10, 23]. Thus, in MS patients with PAC, the use of antiarrhythmic therapy or other treatment methods is indicated as primary prevention of AF in high-risk cases [5–10].

CONCLUSIONS

1. Despite the recommendations for lifestyle modification, only 10.86% of patients achieved the target values of potentially modifiable MS components and other risk factors for AF.

2. The achievement of the target values of the main components of MS, including BMI and/or waist circumference, correlated with the performance of regular aerobic exercises (OR = 8.9), adherence to a diet (OR = 7.5), duration of registration of MS of < 20 years before the start of correction (OR = 12.8), and intake of a glucagon-like peptide-1 receptor agonist (Liraglutide) (OR = 5.4).

3. When a high 5-year risk of primary AF was detected in MS patients with PAC without correction, with incomplete correction, and with the achievement of the target values of potentially modifiable predictors of AF development, the incidence of AF did not differ significantly, which amounted to 93.20%, 88.15%, and 84.95% of the patients, respectively.

4. A decrease in the $R_{\text{CHARGE-AF}}$ index in MS patients with PAC during follow-up determines the efficiency of correction of potentially modifiable predictors of AF development, but its changes do not reflect the degree of risk of AF development.

ADDITIONAL INFORMATION

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