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Predictors of the Development of Associated Clinical Conditions in Working-Age Patients With Cardiovascular Risk Factors in Conditions of High Adherence to Treatment

Aim	To determine predictors for the development of associated clinical conditions (ACC) in patients of working age with cardiovascular risk factors (CVRFs) in the conditions of high compliance with the treatment and healthy lifestyle (HLS).
Material and methods	The study included 364 patients with CVRFs without target organ damage and a history of ACC. Mean age was 42.24±8.08 years. Patients were examined in consistency with the Russian Society of Cardiology (RSC) 2020 guidelines for arterial hypertension and chronic heart failure. The follow-up period was 6.45±0.42 years. 350 patients completed the study, 9 patients died during the follow-up period, and 5 were lost to follow-up. Patients were divided into two groups based on the development of ACC. The first group consisted of 56 (16%) patients with verified ACC, the second group included 294 (84%) patients without ACC.
Results	Regression logistic and correlation analyses confirmed the prognostic significance for the development of ACC by 12 indicators. The risk of ACC in smokers was increased more than 7 times (odds ratio (OR) 7.44, 95% confidence interval (CI): 3.42–16.21), and when type 2 diabetes mellitus (DM) developed, more than 9 times (OR 9.47, 95% CI: 4.36–20.59); with chronic kidney disease (CKD), more than 6 times (OR 6.75, 95% CI: 3.41–13, 37); with a history of COVID-19 (COronaVIrus Disease 2019) pneumonia, 7 times (OR 7.11, 95% CI: 3.04–16.58); with left ventricular hypertrophy (LVH), 6 times (OR 6, 35, 95% CI: 3.14–12.83); with CAVI index>7.2, almost 3 times (OR 2.69, 95% CI: 1.48–4.86); with PVWcf (carotid-femoral pulse wave velocity) >13 m/s, more than 5 times (OR 5.61, 95% CI: 2.79–11.28); with R-AI index (augmentation index) >1, more than 2 times (OR 2.26, 95% CI: 1.3–3.9); and with an increase in the indexed left atrial volume (ILAV) >27 ml/m^2, more than 8 times (OR 8.80, 95% CI: 4.61–16.79). In the presence of polymorphisms in the form of homozygosity for the minor allele of the *AGT* gene (*Thr174Met, rs4762*), the risk of developing ACC increased 14 times (OR 14.13, 95% CI: 4.69–42.57), the *APOE* gene (*Cys130Arg, rs429358*), 11 times (OR 11.18, 95% CI: 4.18–29.93), and in the intron of the *PRARa* gene (*rs4253778*), 8 times (OR 8.11, 95% CI: 3.75–17.53).
Conclusion	The development of ACC in patients with high compliance with treatment and a healthy lifestyle is associated with smoking, type 2 diabetes and CKD, a history of COVID-19 pneumonia, LVH, increased ILAV >27 g/m^2, more pronounced arterial stiffness assessed by an increase in CAVI indices >7.2, R-AI >1, and PWVcf >13 m/s; and with the presence of polymorphism of the *AGT*, *APOE* and *PPARa* genes in the form of homozygosity for the minor allele.

Keywords	Predictors; associated clinical conditions; cardiovascular risk; high compliance with treatment
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Introduction

While early diagnosis of diseases has improved in recent years and effective medical care is more accessible now, cardiovascular diseases (CVDs) remain the leading cause of death in the population [1]. CVDs are also the main causes of death in the active working-age population of Russia (about 30%), including coronary artery disease (CAD) in 46% of cases. Given the fact that the active working-age population makes up more than 50% of the general population and provides the gross national income, which is a main a main macroeconomic indicator of the development of any country, it is especially relevant to study the problem of cardiovascular mortality in this category of patients [2]. CVDs are closely related to

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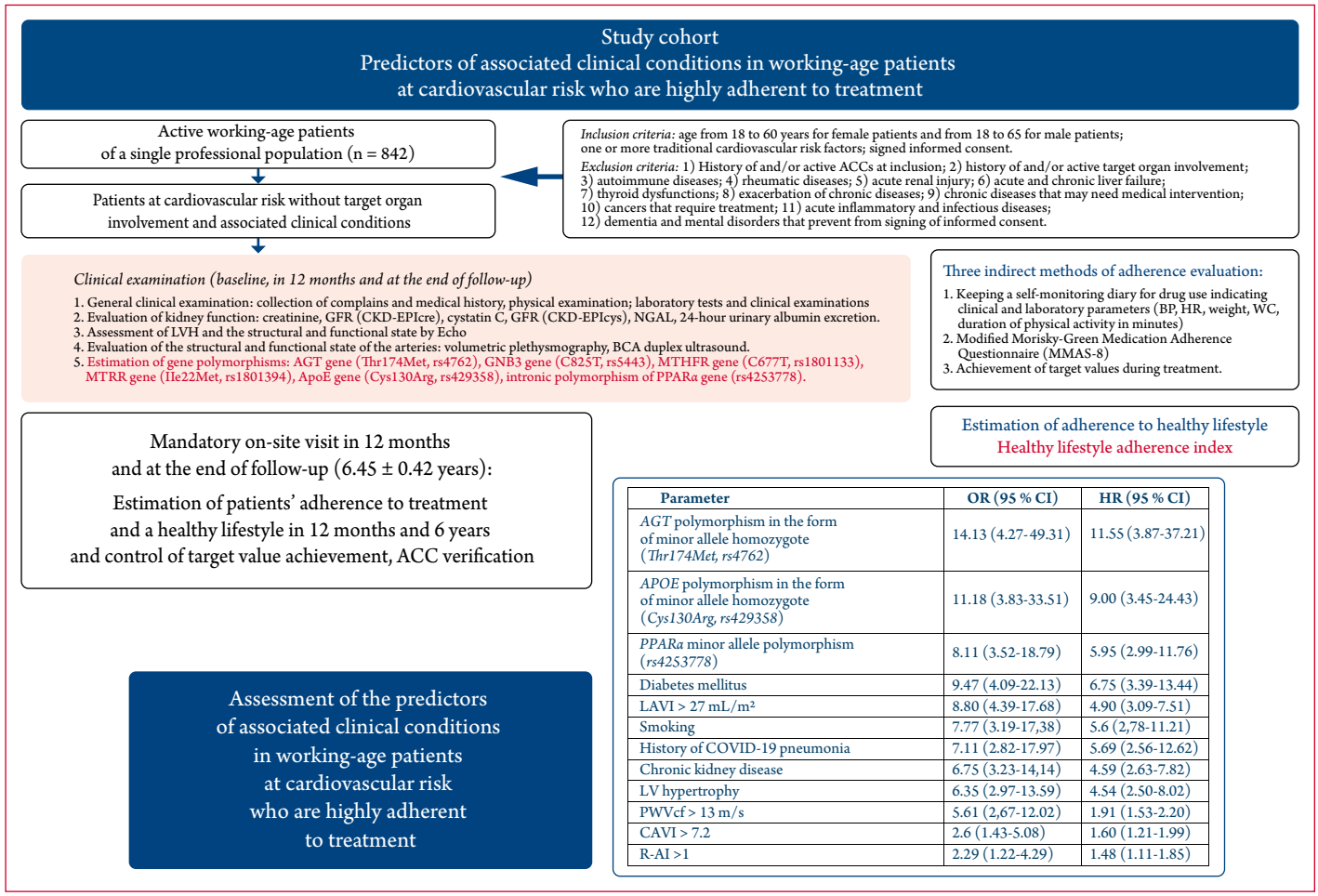
Central Illustration. Predictors of the Development of Associated Clinical Conditions in Working-Age Patients With Cardiovascular Risk Factors in Conditions of High Adherence to Treatment



Parameter	OR (95 % CI)	HR (95 % CI)
AGT polymorphism in the form of minor allele homozygote (*Thr174Met, rs4762*)	14.13 (4.27-49.31)	11.55 (3.87-37.21)
APOE polymorphism in the form of minor allele homozygote (*Cys130Arg, rs429358*)	11.18 (3.83-33.51)	9.00 (3.45-24.43)
PPARa minor allele polymorphism (*rs4253778*)	8.11 (3.52-18.79)	5.95 (2.99-11.76)
Diabetes mellitus	9.47 (4.09-22.13)	6.75 (3.39-13.44)
LAVI > 27 mL/m²	8.80 (4.39-17.68)	4.90 (3.09-7.51)
Smoking	7.77 (3.19-17,38)	5.6 (2,78-11.21)
History of COVID-19 pneumonia	7.11 (2.82-17.97)	5.69 (2.56-12.62)
Chronic kidney disease	6.75 (3.23-14,14)	4.59 (2.63-7.82)
LV hypertrophy	6.35 (2.97-13.59)	4.54 (2.50-8.02)
PWVcf > 13 m/s	5.61 (2,67-12.02)	1.91 (1.53-2.20)
CAVI > 7.2	2.6 (1.43-5.08)	1.60 (1.21-1.99)
R-AI >1	2.29 (1.22-4.29)	1.48 (1.11-1.85)

ACC, associated clinical condition; LVH, left ventricular hypertrophy; GFR, glomerular filtration rate; LA, left atrium; BP, blood pressure; BSA, body surface area; HR, heart rate; BCA, brachiocephalic artery; WC, waist circumference; DM, diabetes mellitus; CKD, chronic kidney disease; CKD-EPIcre, chronic kidney disease epidemiology collaboration creatinine-based; CKD-EPIcys, chronic kidney disease epidemiology collaboration cystatin c-based; NGAL, neutrophil gelatinase-associated lipocalin; COVID-19, coronavirus disease 2019; AGT, angiotensinogen; GNB, guanine nucleotide-binding protein; MTHFR, methylenetetrahydrofolate reductase; MTRR, methionine synthase reductase; ApoE, apolipoprotein E; PPARα, peroxisome proliferator-activated receptor alpha ; CAVI, cardio-ankle vascular index; R-AI, augmentation index; PWVcf, carotid femoral pulse wave velocity; MMAS, Modified Morisky-Green Medication Adherence Questionnaire.

lifestyle and risk factors (RFs) such as smoking, unhealthy diet, lack of physical activity, alcohol abuse, overweight and obesity, hypertension, and psychosocial factors. Therefore, primary prevention aimed at early detection and correction of cardiovascular RFs is one of the main strategies for solving the problem of cardiovascular mortality [1]. At the same time, it is important that most deaths from CVDs can be prevented by eliminating or correcting the identified RFs by adhering to a healthy lifestyle and through medical interventions [3].

Low adherence to a healthy lifestyle and treatment was shown to be one of the main reasons for the lack of efficacy of medical care and for poor prognosis [4, 5]. The 10-year trend in achieving blood pressure (BP) and blood lipid profile targets in working-age patients remains low [6]. There is no real-world information on the contribution of high adherence to treatment in reducing the risk of development and progression of coronary artery disease (CAD), myocardial infarction (MI), stroke, chronic heart failure (CHF), type 2 diabetes mellitus (DM), especially in active working-age population. Randomized clinical trials, in which high compliance is a mandatory inclusion criterion, can be used as a model of high adherence to treatment and components of healthy lifestyle. However, there are significant limitations in their implementation: a certain type of treatment, a special selected population, exclusion of the use of certain drugs, etc., which does not always allow using the results obtained [7]. The creation of a model of high adherence to treatment and components of healthy lifestyle based on financial incentives, therapeutic training of patients, correction of motivation and habits, in order to conduct primary cardiovascular prevention in

working-age individuals at cardiovascular risk, is a highly relevant but largely unexplored task of cardiology.

Traditional cardiovascular RFs and lifestyle indicators interacting with genetic features can accelerate the development of CVDs [1, 8, 9]. However, the contribution of gene polymorphism to the development of cardiovascular RFs and associated clinical conditions (ACCs) in high adherence to treatment is unclear. Genetic markers are not used in any cardiovascular risk score.

The objective of this study is to determine the predictors of ACCs in working-age patients at cardiovascular risk who are very adherent to treatment and a healthy lifestyle during long-term follow-up.

Material and Methods

The prospective observational cohort clinical study was implemented under the Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the ethics committee. All subjects signed the informed consent before being included in the study.

A total of 842 working-age individuals were examined who serve in the management apparatus of an industrial enterprise with similar working conditions and without occupational hazards; 380 patients were selected who met the inclusion exclusion criteria.

Inclusion criteria: age from 18 to 60 years in female patients and from 18 to 65 in male patients; one or more traditional cardiovascular risk factors; signed informed consent.

Exclusion criteria:

1) history of and/or active ACCs at inclusion;
2) history of and/or active target organ involvement;
3) autoimmune diseases;
4) rheumatic diseases;
5) acute kidney injury;
6) acute and chronic liver failure;
7) thyroid dysfunctions;
8) exacerbation of chronic diseases;
9) chronic diseases that may need medical intervention;
10) cancers that require treatment;
11) acute inflammatory and infectious diseases;
12) dementia and mental disorders that prevent from signing of informed consent.

A cohort of 364 patients was selected from 380 people who were ready to follow the recommendations for treatment and a healthy lifestyle.

Traditional cardiovascular RFs and 7 components of a healthy lifestyle were assessed in accordance with the guidelines of the World Health Organization: no smoking, no alcohol abuse, low physical activity, obesity, excess salt intake, following dietary recommendations, absence of hypertension, or achievement of BP targets.

The following traditional and non-traditional cardiovascular RFs were estimated: age, family history, fasting plasma glucose, dyslipidemia, hyperuricemia, labor stress, COVID-19 at any time, single-nucleotide polymorphisms (SNP) of the *AGT* gene (T*hr174Met, rs4762*), the *GNB3* gene (*C825T, rs5443*), the *MTHFR* gene (*C677T, rs1801133*), the *MTRR* gene (*Ile22Met, rs1801394*), the *APOE* gene (*Cys130Arg, rs429358*), and in the *PPARa* gene intron (*rs4253778*). The following genotypes were identified: major allele homozygosity, heterozygosity, minor allele homozygosity: C/C, C/T, T/T for the *AGT* gene; C/C, C/T, T/T for the *GNB3* gene; C/C, C/T, T/T for the *MTHFR* gene; A/A, A/G, G/G for the *MTRR* gene; T/T, T/C, C/C for the *APOE* gene; G/G, G/C, C/C for the *PPAR* gene, respectively. Genomic deoxyribonucleic acid (DNA) isolated from venous blood was used for the assay. Gene polymorphism was studied by real-time polymerase chain reaction in the CFX 96 TOUCH system (Bio-Rad Laboratories, USA) using ready primer sets and production probes by Thermo Fisher Scientific Applied Biosystems, USA. K-Sorb reagent sets (LLS Syntol, Russia) were used to isolate DNA.

All included patients were trained to follow drug treatment recommendations and adhere to a healthy lifestyle. Fear of losing high wages and bonuses in case of failure to follow the recommendations was a financial incentive for adherence to treatment and a healthy lifestyle.

All subjects were recommended to keep self-monitoring diaries for drug use and clinical indicators.

Mandatory phone calls were made per every six months to monitor the implementation of medical recommendations and a healthy lifestyle, treatment adherence, achievement of the target indicators of cardiovascular RFs, treatment was corrected if necessary or at the patient's request, on-site visits were made, texting and emailing were allowed.

Mandatory on-site visits were made in 12 months and at the end of follow-up to control diaries, achievement of targets of cardiovascular RFs and a healthy lifestyle, assess adherence to treatment and a healthy lifestyle, repeated laboratory tests and clinical examinations and the registration of cardiovascular RFs, newly identified target organ involvement and ACCs: such diseases as ischemic and/or hemorrhagic acute cerebrovascular accident (CVA), transient ischemic attack (TIA); CAD: stable angina pectoris, MI, percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG); atrial fibrillation (AF) and/or atrial flutter (AFL); CHF, including with preserved left ventricular ejection fraction (LVEF); imaging of atherosclerotic plaques with ≥ 50% stenosis; CKD with estimated

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glomerular filtration rate (eGFR (CKD-EPIcre)) <30 mL/min/1.73 m^2 [10]. The development of CKD with eGFR > 30 mL/min/1.73 m^2 and/or type 2 DM without target organ involvement was considered as a newly identified comorbidity.

The duration of follow-up was 6.45 ± 0.42 years.

Three indirect methods were used to assess patients' adherence to treatment: keeping a diary of self-control for drug use with registering of clinical and laboratory indicators (daily measurement of resting BP, heart rate (HR), weight, waist circumference (WC), duration of physical activity in minutes, control of fasting capillary blood glucose in the morning using a glucometer for some patients); modified Morisky-Green Medication Adherence Questionnaire (MMAS-8) [11], achievement of target values during treatment. Adherence to a healthy lifestyle was assessed using the Healthy Lifestyle Adherence Index (HLAI) [5].

BP was measured and 24-hour BP monitoring was conducted using the Card (X) Plore monitor (Meditech, Hungary) for all patients. Hypertension was verified according to the guidelines of the Russian Society of Cardiology for the management of hypertension (2020) [12].

The structural and functional state of the heart was assessed using echocardiography by determination of LVEF by the Simpson method, left atrial volume index (LAVI), left ventricular mass index (LVMI), and LV diastolic function. Left ventricular hypertrophy (LVH) and LV diastolic dysfunction (LVDD) were verified according to the guidelines of the Russian Society of Cardiology for the management of hypertension and CHF (2020).

Serum creatinine and cystatin C were determined and GFR was calculated using the CKD-EPIcre and CKD-EPIcys formulas to evaluate renal function [10]. Neutrophil gelatinase-associated lipocalin (NGAL) and 24-hour urinary albumin/protein excretion were also determined.

Arterial stiffness was assessed by volumetric plethysmography on the VaSera VS-1000 device (Fucuda Denshi, Japan) with the determination of cardio-ankle vascular index (CAVI), carotid-femoral pulse wave velocity (PWVcf), right upper arm-right ankle pulse wave velocity (R-PWV) and right upper arm-left ankle pulse wave velocity (L-PWV), aortic pulse wave velocity (PWVa), carotid artery pulse wave velocity (C-PWV), and the augmentation index (R-AI).

The data obtained were processed in Statistica 13.5 and Medcalc 11.5.0. Normally distributed quantitative variables were presented as the arithmetic means and standard deviations (M ± SD); non-normally distributed quantitative variables were expressed as the medians and the lower and upper quartiles (Me [LQ; UQ]) or 95% CI. The Mann-Whitney test and the Student's test were used to compare non-normally and normally distributed quantitative variables, respectively. Chi-squared test was used to compare qualitative variables. Spearman's correlation analysis was used to study the relationship between quantitative variables, and 2×2 contingency tables were used to study the relationship between qualitative indicators; chi-squared test and the achieved level of significance were calculated using Yates's correction for continuity. Chuprov's mutual contingency coefficient was used to assess the relationship of qualitative variables. The differences were considered statistically significant at $p < 0.05$.

The prognostic significance of ACC risk factors for was assessed using multivariate logistic regression analysis. ROC analysis was performed with the calculation of area under curve (AUC) > 0.5 at $p < 0.05$ to assess the quality of logistic regression for quantitative variables. The cut-off threshold was determined and its sensitivity and specificity were assessed for statistically significant predictive quantitative indicators. Odds ratios (OR) and hazard ratios (HR) were calculated for all qualitative indicators.

Results

A total of 350 patients completed the study: 9 patients died during the follow-up period and 5 patients were lost to follow-up. Patients were divided into 2 groups depending on the development of ACCs: Group 1 consisted of 56 (16.0%) patients with verified ACCs, Group 2 included 294 (84.0%) patients without ACCs.

At baseline, patients of the groups compared did not differ statistically significantly in the main clinical and demographic characteristics, cardiovascular RFs, comorbidities, concomitant drug therapy, echocardiographic findings, and functional state of the kidneys and arteries. At the same time, patients with ACCs were older ($p<0.001$) and smoked more ($p<0.001$).

Patient adherence was not assessed at baseline, since 1 to 6 cardiovascular RFs were found in 90.3% of patients for the first time – recommendations for correction were given at inclusion in the study. Only 6.8% of patients with hypertension took occasionally antihypertensive drugs and 3.4% of patients administered statins. In 12 months and throughout the study, all patients showed high adherence to treatment and a healthy lifestyle without statistically significant differences between the groups (Table 1).

The structure of the ACCs verified during the follow-up period is presented in Table 2.

Table 1. Patients' adherence to treatment and a healthy lifestyle in the groups compared in 12 months and at the end of the study (n = 350)

Parameter	Group 1 – patients with ACCs (n = 56)	Group 2 – patients without ACCs (n = 294)	p
High adherence according to MMAS-8, n/% (in 12 months)	48/85.7 %	251/85.37 %	0.889
High adherence according to MMAS-8, n/% (at the end of the study)	49/87.5 %	253/86.05 %	0.774
High adherence according to HLAI, n/% (in 12 months)	47/83.93 %	252/85.71 %	0.729
High adherence according to HLAI, n/% (at the end of the study)	49/87.5 %	256/87.07 %	0.931

ACC, associated clinical condition; MMAS-8, 8-question Morisky Medication Adherence Scale; HLAI, healthy lifestyle adherence index

Table 2. Associated clinical conditions detected during the follow-up period (n = 56)

Nosology	Incidence rate
CVA, n/%	5/8.93 %
TIA, n/%	2/3.57 %
CAD, n/%	41/73.21 %
Stable angina, n/%	32/57.14 %
Myocardial infarction, n/%	8/14.29 %
PCI, n/%	2/3.57 %
Coronary artery bypass grafting, n/%	3/5.36 %
Atrial fibrillation/atrial flutter, n/%	5/8.93 %
Chronic heart failure, n/%	5/8.93 %
Peripheral atherosclerotic stenosis, n/%	4/7.14 %

CVA, acute cerebrovascular accident; TIA, transient ischemic attack; CAD, coronary artery disease; PCI, percutaneous coronary intervention.

Moreover, new comorbidities were detected, such as type 2 DM (9.2%), CKD (12.9%), COVID-19 (48.3%), and COVID-19 pneumonia (6.3%). The compared groups differed statistically significantly in the frequency of newly diagnosed DM: 32.1% vs 4.8% (p<0.001), CKD: 37.5% vs 8.2%; p < 0.001). Patients of Group 1 had COVID-19 pneumonia more often (p<0.001).

Comparative characteristics of clinical and demographic indicators at the end of the study are presented by groups are presented in Table 3.

There were significant differences between the groups in age (p<0.001), body mass index (BMI) (p=0.033), and smoking frequency (p<0.001) at the end of follow-up period. Patients with ACCs took antiplatelet drugs and anticoagulants, beta-blockers, and glucose-lowering therapy statistically significantly more often.

Patients with ACCs had higher levels of creatinine (p=0.008) and GFR (CKD-EPIcre) (p = 0.002), cystatin C (p<0.001) and GFR (CKD-EPIcys) (p<0.001) (Table 4).

Patients of the groups compared did not differ significantly in the frequency of polymorphisms of the *GNB3*, *MTHF* and *MTRR*, *AGT* and *APOE* genes in the heterozygous form and in the form of major allele homozygotes. There was a higher incidence of the T / T genotype of the *AGT* gene (p<0.001), the C / C genotype of the *ApoE* gene (p<0.001), the PPARα genotype with a higher incidence of minor allele homozygote and a lower incidence of major allele homozygote (p<0.001 and p=0.018, respectively) in patients with ACCs (Table 5).

Patients with ACCs had statistically significantly more severe changes in the arteries and the heart as assessed by

Table 3. Clinical and demographic characteristics of patients in the groups compared at the end of the study(n = 350)

Parameter	Group 1. Patients with ACCs (n = 56)	Group 2. Patients without ACCs (n = 294)	p
Age, years	57.5 [55.7; 59.3]	50.5 [49.4; 51.7]	< 0.001
Sex, M/F, n/%.	M 40/71.4 %; F 16/28.6 %	M 176/59.9 %; F 118/40.1 %	0.103
BMI, kg/m²	27.12 [25.77; 29.13]	25.61 [23.01; 26.11]	0.033
WC in female patients, cm	89.3 [87.68; 92.87]	88.22 [85.96; 91.31]	0.884
WC in male patients, cm	92.35 [87.39; 102.79]	90.72 [87.1; 101.10]	0.889
SBP, mm Hg	124.81 [122.10; 130.60]	121.90 [119.50; 126.60]	0.352
DBP, mm Hg	79.91 [76.51; 83.14]	78.20 [74.11; 80.43]	0.729
HR, bpm	67.50 [62.31; 70.52]	66.50 [61.51; 69.31]	0.927
Smoking, n/%	16/28.57 %	15/5.10 %	< 0.001
Smoking index, pack-years	14.12 [9.87; 15.89]	10.1 [8.74; 13.43]	0.587

ACC, associated clinical condition; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic arterial hypertension.

such indicators as R-PWV, L-PWV, PWVcf, R-AI, CAVI, LVMI, LAVI, LVEF, the presence of LVH and LVDD (Table 6).

The correlation analysis revealed moderate direct relationships between the presence of ACCs and BMI (r=0.36; p<0.05), creatinine (r=0.32; p<0.05), cystatin C

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Table 4. Functional state of kidneys in the groups compared at the end of the study(n = 350)

Parameter	Group 1. Patients with ACCs (n = 56)	Group 2. Patients without ACCs (n = 294)	p
Serum creatinine, μmol/L	81.47 [76.51; 86.43]	74.0 [71.73; 77.30]	0.008
GFR (CKD-EPIcre), mL/min/1,73 m²	88.50 [83.90; 94.11]	98.80 [96.04; 101.25]	0.002
Cystatin C, ng/mL	1016.17 [947.60; 1084.74]	883.59 [842.96; 924.21]	< 0.001
GFR (CKD-EPIcys), mL/min/1,73 m²	79.3 [72.88; 85.71]	93.59 [88.97; 98.21]	< 0.001
NGAL, pg/mL	1.73 [1.37; 2.08]	1.42 [1.22; 1.63]	0.155
Albumin excretion in urine, mg/day	15.5 [9.94; 20.07]	14.3 [8.49; 19.59]	0.064

ACC, associated clinical condition; GFR, glomerular filtration rate; CKD-EPIcre, chronic kidney disease epidemiology collaboration creatinine-based, CKD-EPIcys, chronic kidney disease epidemiology collaboration cystatin c-based, NGAL, neutrophil gelatinase-associated lipocalin.

Table 5. Gene polymorphism in the groups compared (n = 350)

Gene polymorphism	Group 1. Patients with ACCs (n = 56)	Group 2. Patients without ACCs (n = 294)	p
Minor allele homozygosity, *AGT* gene (*Thr174Met, rs4762*) T/T genotype, n/%	11/19.64 %	5/1.7 %	< 0.001
Minor allele homozygosity, *ApoE* gene (*Cys130Arg, rs429358*) C/C genotype, n/%	12/21.43 %	7/2.38 %	< 0.001
Major allele homozygosity, *PPARα* gene (*rs4253778*) G/G genotype, n/%	33/58.93 %	219/74.49 %	0.018
Minor allele homozygosity, *PPARα* gene (*rs4253778*), C/C genotype, n/%	17/30.36 %	15/5.1 %	< 0.001

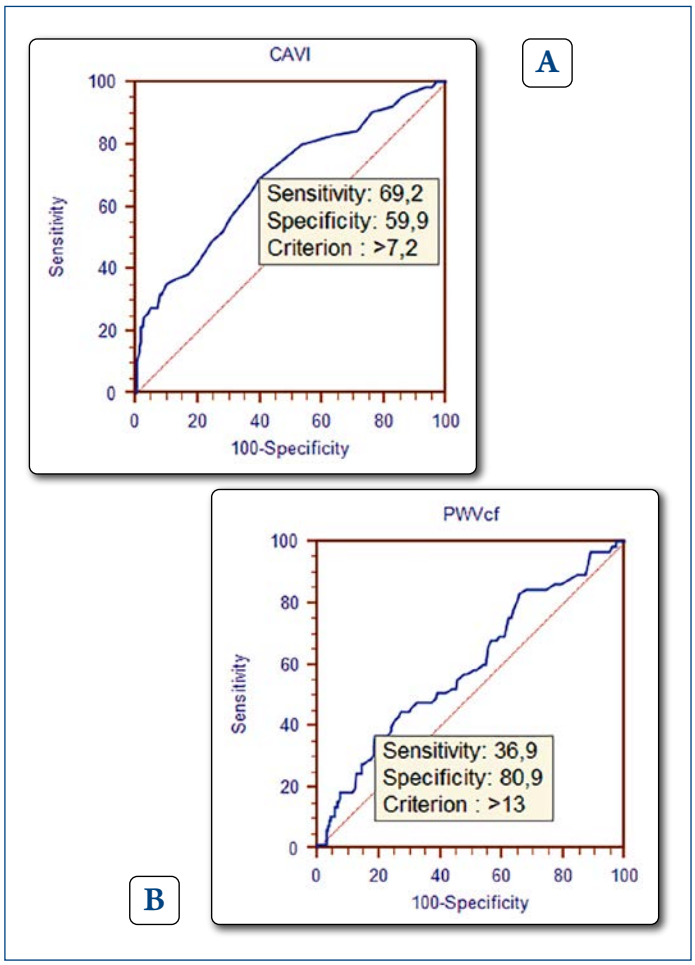
ACC, associated clinical condition; AGT, angiotensinogen; APOE, apolipoprotein E; PPARα, peroxisome proliferator-activated receptor alpha.

(r=0.47; p < 0.05), CAVI (r = 0.39; p < 0.05), PWVcf (r=0.33; p<0.05), R-AI (r = 0.32; p < 0.05), LVEF (r=0.35; p<0.05), and LAVI (r = 0.33; p < 0.05). Moderate inverse relationship between the presence of ACCs and GFR (CKD-EPIcys) was also observed (r = –0.42; p<0.05).

The ROC curve showed prognostic significance of only 4 of 9 quantitative indicators correlated with the development of ACCs and considered as candidate predictors of ACCs: CAVI, PWVcf, R-AI, LAVI. The cut-off point of 7.2 was obtained for CAVI (AUC=0.69, p=0.038). CAVI > 7.2 can serve as a predictor of ACCs in patients with high adherence to treatment and a healthy lifestyle with sensitivity of 69.2% and specificity of 59.9% (p<0.05) (Figure 1 A). The ROC curve showed the cut-off value of 13 m/s for PWVcf (AUC = 0.60, p=0.039). PWVcf > 13 m/s can serve as a predictor of ACCs in patients with high adherence to treatment and a healthy lifestyle with sensitivity of 36.9% and specificity of 80.9% (p < 0.05) (Figure 1B).

The cut-off point of 1 was obtained for R-AI using the ROC-curve (AUC = 0.64, p=0.038). R-AI > 1 can serve as a predictor of ACCs in patients with high adherence to

Figure 1. ROC curve for CAVI (**A**) and PWVcf (**B**) as predictors of ACCs



ROC, receiver operating characteristic; CAVI, cardio-ankle vascular index; PWVcf, carotid femoral pulse wave velocity; ACC, associated clinical condition.

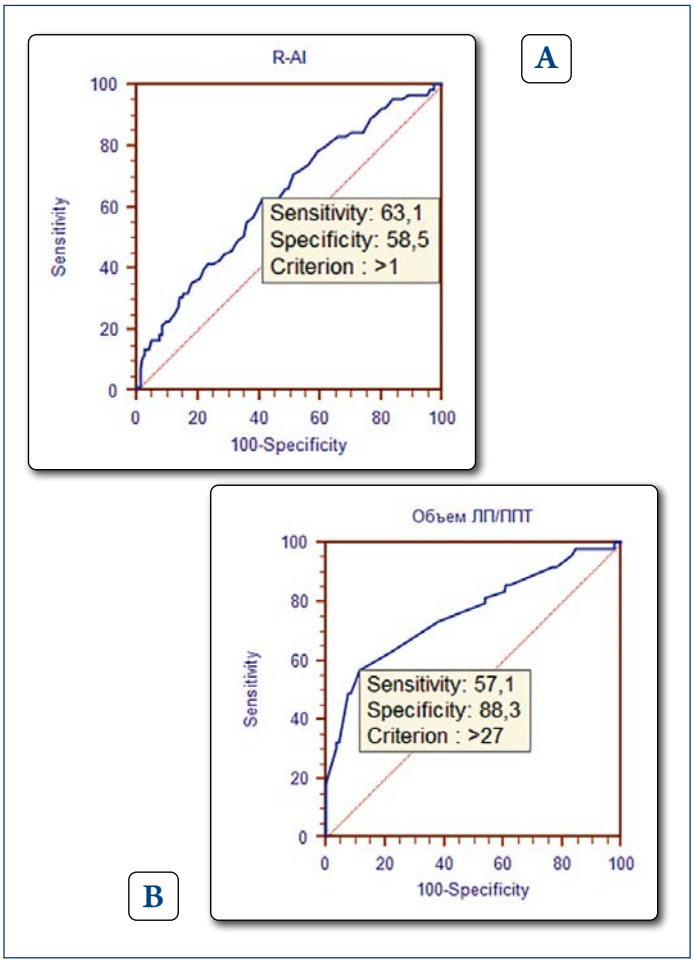
treatment and a healthy lifestyle with sensitivity of 63.1% and specificity of 58.5% (p<0.05) (Figure 2A).

The ROC curve showed the LAVI cut-off value of 27 mL/m² (AUC=0.76, p=0.043). LAVI >27 mL/m² can serve as a predictor of ACCs with sensitivity of 57.1% and specificity of 88.3% (p < 0.05) (Figure 2B).

The assessment of the relationship of qualitative indicators showed moderate direct relationships between the presence of ACCs and LVH (K = 0.30; p<0.05), type 2 DM (K = 0.35; p<0.05), CKD (K = 0.32; p<0.05), COVID-19 pneumonia (K = 0.30; p < 0.05), the *AGT* gene polymorphism in the form of minor allele homozygote (K=0.31; p<0.05), the *ApoE* gene polymorphism in the form of minor allele homozygote (K = 0.31; p<0.05), intron polymorphism of the *PPRARa* gene in the form of minor allele homozygote (K = 0.32; p < 0.05).

In the logistic regression analysis in the setting of high adherence to treatment and a healthy lifestyle, 12 qualitative indicators confirmed the prognostic significance for the risk of ACCs: smoking, CAVI >7.2, PWVcf >13 m/s, R-AI>1, LAVI>27 mL/m², the presence

Figure 2. ROC curve for R-AI (**A**) and LAVI (**B**) as predictors of ACCs



ROC, receiver operating characteristic; R-AI, augmentation index; LAVI, left atrial volume index; ACC, associated clinical condition.

Table 6. Structural and functional state of arteries and the heart in the groups compared at the end of the study (n = 350)

Parameter	Group 1. Patients with ACCs (n = 56)	Group 2. Patients without ACCs (n = 294)	P
R-PWV, m/s	14.09 [13.51; 14.67]	12.91 [12.50; 13.11]	< 0.001
L-PWV, m/s	13.72 [13.21; 14.16]	12.72 [12.41; 13.02]	< 0.001
C-PWV, m/s	5.41 [4.48; 6.31]	5.70 [5.28; 6.11]	0.234
PWVao, m/s	7.92 [7.03; 8.72]	7.27 [6.83; 7.66]	0.132
PWVcf, m/s	11.97 [9.96; 12.97]	10.78 [10.32; 11.21]	0.009
R-AI	1.09 [1.04; 1.16]	1 [0.97; 1.02]	< 0.001
CAVI	7.99 [7.61; 8.29]	7.25 [7.16; 7.34]	< 0.001
LVMI, g/BSA, g/m²	115.32 [109.21; 121.40]	102.70 [99.31; 106.10]	< 0.001
LVMI, g/m$^{2.7}$	54.31 [51.40; 60.11]	48.21 [45.90; 50.11]	< 0.001
LVH, n/%	19/33.93 %	22/7.48 %	< 0.001
LA volume, mL	48.50 [46.31; 50.43]	42.41 [41.42; 43.93]	< 0.001
LAVI, mL/m²	28.10 [26.90; 29.31]	24.45 [24.02; 25.03]	< 0.001
LVDD, n/%	14/25 %	42/14.29 %	0.046
LVEF (Simpson), %	63.62 [62.21; 65.30]	65.01 [64.02; 66.03]	0.002

ACC, associated clinical condition; R-PWV, right upper arm-right ankle pulse wave velocity; L-PWV, right upper arm-left ankle pulse wave velocity; C-PWV, carotid pulse wave velocity; PWVao, aortic pulse wave velocity; PWVcf, carotid-femoral pulse wave velocity; R-AI, augmentation index; CAVI, cardio-ankle vascular index; LVMI, left ventricular mass index; BSA, body surface area; LVH, left ventricular hypertrophy; LA, left atrium; LAVI, left atrial volume index; LVDD, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction.

of LVH, type 2 DM, and CKD, history of COVID-19 pneumonia and polymorphisms of the *AGT*, *APOE*, and *PPARa* genes in the form of homozygote (Table 7).

Discussion

The idea of creating a model of high adherence to treatment and a healthy lifestyle in working-age individuals arose for two reasons. On the one hand, a reduction in the risk of developing MI, stroke, CHF, and all-cause and cardiovascular mortality was shown in clinical studies, which represent a model of high adherence to a certain type of treatment in a certain patient population even despite these limitations [13, 14]. On the other hand, in some groups of the active working-age population involved in the operation of several of industrial sites, employers have already created

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conditions for adherence to a healthy lifestyle and and cardiovascular RFs correction, which are indirectly associated with fear of a decrease in consistently high wages, deprivation or reduction of bonuses and even termination of employment due to non-adherence to a healthy lifestyle and treatment, which in some cases is defined by the contract. Financial incentives have a major influence on increasing treatment adherence [15].

Genetic screening was carried out in the study since the great significance of genetic polymorphisms in the development of CVDs was demonstrated in recent years [16]. In our study, polymorphisms in the form of minor allele homozygotes showed the maximum contribution to the development of ACCs in patients with high adherence to a healthy lifestyle and treatment. A systematic review of the genetic predictors of atherosclerosis confirmed that atherosclerosis has a significant hereditary component; research of the genetics of CVDs continues but doubts often outweigh certainties [17]. The large amount of evidence allows identifying 5 potentially important pathways that genetic research can specifically target: lipoprotein metabolism, inflammation, renin-angiotensin-aldosterone system (RAAS), platelet function, blood clotting, and fibrinolysis. In our study, the single nucleotide polymorphisms of the *AGT*, *GNB3*, *MTHFR*, *MTRR*, *APOE*, *PPARa* genes associated with the development and progression of hypertension, dyslipidemia, type 2 DM, LVH, CKD, atherosclerosis, and CAD were found in 14.2% of working-age individuals, which on average corresponds to the available data. The prevalence of the gene polymorphisms studied is fairly high in the European population. The *AGT* gene polymorphism, T allele occurs in up to 41%, the *GNB3* gene, T allele in up to 31%, the *MTHFR* gene, C allele in 10%, the *MTRR* gene, G allele in up to 54%, the *APOE* gene, E2 allele in 11%, E4 in 17%, the *PPARa* gene in 12% [18–22].

Many studies showed that *APOE* plays an important role in lipid metabolism. It is this gene's polymorphism that can be associated with higher levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides, which in turn increases the risk of developing CVDs [23]. Moreover, there is evidence that the *APOE* gene polymorphism may be associated with elevated C-reactive protein [24]. Therefore, a certain "genetic status" contributes to the development of CVDs due to subclinical nonspecific inflammation. In this regard, the *APOE* gene polymorphism can be considered as one of the markers of CVDs, which was shown in our study.

Peroxisome proliferator-activated α receptors have an anti-inflammatory effect in the development of CVDs mainly by inhibiting pro-inflammatory signaling pathways and improving the lipid profile. Moreover, the *PPARa* gene also modulates the activity of endothelial nitric oxide synthase and reloads the RAAS to regulate vascular tone [25]. Thus, the *PPARa* gene is associated with the regulation of inflammation and oxidative stress, therefore its polymorphism in the form of minor allele homozygote is associated with endothelial dysfunction and dyslipidemia, and, thus, the development of atherosclerosis and CVDs [22]. In this regard, this gene's polymorphism can be considered as a predictor of ACCs.

One of the most difficult health related factors to control for our patients was smoking cessation, and the percentage of smokers in the group of patients with ACCs was statistically significantly higher than in patients without ACCs. Indeed, only 53% of patients quit smoking even among middle-aged patients with a history of CVDs participating in cardiac rehabilitation programs, as shown in a meta-analysis of 18 observational studies [26]. However, smoking cessation is an independent predictor of improved prognosis in primary prevention of CVDs. Thus, according to over 26.4 years of observation in the Framingham study, quitting smoking

Table 7. Odds ratio and hazard ratio for predictors of associated clinical conditions

Parameter	OR (95 % CI)	HR (95 % CI)
AGT polymorphism in the form of *AGT* minor allele homozygote (*Thr174Met, rs4762*)	14.13 (4.27–49.31)	11.55 (3.87–37.21)
APOE polymorphism in the form of minor allele homozygote (*Cys130Arg, rs429358*)	11.18 (3.83–33.51)	9.00 (3.45–24.43)
PPARa minor allele polymorphism (*rs4253778*)	8.11 (3.52–18.79)	5.95 (2.99–11.76)
Diabetes mellitus	9.47 (4.09–22.13)	6.75 (3.39–13.44)
LAVI >27 mL/m²	8.80 (4.39–17.68)	4.90 (3.09–7.51)
Smoking	7.77 (3.19–17.38)	5.6 (2.78–11.21)
History of COVID-19 pneumonia	7.11 (2.82–17.97)	5.69 (2.56–12.62)
Chronic kidney disease	6.75 (3.23–14.14)	4.59 (2.63–7.82)
LVH	6.35 (2.97–13.59)	4.54 (2.50–8.02)
PWVcf > 13 m/s	5.61 (2.67–12.02)	1.91 (1.53–2.20)
CAVI > 7.2	2.6 (1.43–5.08)	1.60 (1.21–1.99)
R-AI >1	2.29 (1.22–4.29)	1.48 (1.11–1.85)

AGT, angiotensinogen; *APOE*, apolipoprotein E; *PPARa*, peroxisome proliferator-activated receptor alpha; LAVI, left atrial volume index, LVH, left ventricle hypertrophy, PWVcf, carotid femoral pulse wave velocity; CAVI, cardio-ankle vascular index; R-AI, augmentation index.

within 5 years was associated with a 39% reduction in the hazard ratio (HR) of developing CVDs (95% CI: 0.49–0.76), but the CVD HR, compared to smoking-naive individuals was 25% higher (95% CI: 0.98–1.60) and remained high for another 15 years after quitting smoking [27].

Despite the high adherence to treatment by the end of follow-up, every third patient in the ACC group developed type 2 DM (32.1%), which increased the risk of developing ACCs more than 9-fold. A meta-analysis of 7 RCTs (n=4090) showed that high adherence to healthy lifestyle recommendations, even in individuals with impaired glucose tolerance, could reduce HR of type 2 DM by 47% (95% CI: 0.41–0.67) [28]. But its incidence still remains high and is 60.3% within 1–6 years of follow-up due to the probable preservation of other additional cardiovascular RFs, such as hyperuricemia, increased concentration of leptin and decreased adiponectin, genetically determined obesity, and some polymorphisms of the *ACE*, *APOA-I*, *APOE*, adiponectin, and other genes [29].

In our study, LAVI increase within within the normal range (>27 mL/m^2) was associated with the 8-fold chance of developing ACCs. We assume that this is due to the formation of atrial cardiomyopathy rather than LA dimensions, which is characterized by functional disorders of the organ and, in the early stages, by molecular changes in the atrial cells [30].

The study did not find a correlation between a history of COVID-19 and the risk of developing ACCs, but a history of COVID-19 pneumonia increased the risk of developing ACCs more than 7-fold. This relationship is well established, including in young and middle-aged people, even those at low to moderate cardiovascular risks [31].

The relationship of LVH, CKD, and arterial stiffness with the development of ACCs is well known, and it was shown in our study that it persists during high adherence to treatment and a healthy lifestyle. The risk of cardiovascular death and events associated with hospitalization for CHF remains high in treated patients with hypertension not only as LVH progresses but also in the absence of its regression during antihypertensive treatment, as shown in the observational study by Kim et al. [32].

Ortiz et al. showed the contribution of CKD to CVDs development and the need to include CKD diagnosis in the assessment of cardiovascular risk [33].

PWVcf, CAVI, and augmentation index, which are well known but not studied in high treatment adherence, were shown as vascular predictors of ACCs in our study [34]. A meta-analysis by Zhong et al. showed that a 1 m/s increase in PWVcf was correlated with high HR of cardiovascular events and deaths and confirmed that the prognostic value of PWVcf was higher in patients at higher cardiovascular risk [35].

The study was limited by the absence of research into the relationship between the risk of ACCs and the indicators of collagen formation, the abnormalities of which may be one of the most important mechanisms of CVD development in the early stages. Moreover, we did not take into consideration the phenotypes of hypertension, which also requires further research and discussion.

Conclusion

Creating a model of high adherence to treatment and a healthy lifestyle in working-age individuals without a history of target organ involvement and ACCs during long-term follow-up showed that the polymorphism of the *AGT*, *APOE*, and *PPARα* genes in the form of minor allele homozygotes, and smoking, type 2 DM, CKD, COVID-19 pneumonia, LVH in combination with elevated LAVI > 27 g/m^2 and arterial remodeling with increased CAVI > 7.2, R-AI > 1, PWVcf > 13 m/s should be considered the predictors of the maximum risk of ACCs.

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