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Effect of *C-344T* polymorphism of aldosterone synthase gene on variability of antihypertensive therapy with angiotensin II receptor blockers: open randomized controlled clinical trial

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The effectiveness of the antihypertensive therapy may be associated with genetic factors that affect not only the degree of a blood pressure elevation but also predetermine an interindividual variability in response to the antihypertensive treatment.

The aim of the work was to study pharmacodynamic indices of the effectiveness of therapy with angiotensin II receptor blockers (ARBs) in the form of monotherapy and as a part of combined drugs in patients with an arterial hypertension (AH) depending on genetic features of patients – a polymorphism of the gene encoding aldosterone synthase, the *C-344T* polymorphism.

Materials and methods. The study included 179 patients of the Moscow region with a newly diagnosed 1–2-degree AH (141 (78.8%) women and 38 (21.2%) men) aged from 32 to 69 years who had been randomly allocated to treatment groups with irbesartan and valsartan in the form of the mono- or combined therapy with hydrochlorthiazide by simple randomization. After 3 weeks of pharmacotherapy, the presence of the genetic *rs1799998 (C-344T)* polymorphism of the aldosterone synthase gene, *CYP11B2*, and the minimum equilibrium concentration of angiotensin receptor blockers (ARBs) were determined.

Results. *TT* homozygotes in the irbesartan group were characterized by a lower level of the blood pressure (BP) target achievement after 3 weeks of pharmacotherapy and a higher frequency of the need to intensify the antihypertensive therapy compared with *CT* and *TT* genotypes. Among the patients taking valsartan, the carriers of the *TT* genotype were characterized by a higher frequency of achieving the target BP after 3 weeks of pharmacotherapy compared to the *CC* (p <0.001) and *CT* genotypes (p=0.084). Herewith, at the end of the study, according to the results of the office BP measurement and daily BP monitoring (DBPM), the achievement of the target BP values was not significantly associated with *CYP11B2 C-344T* genotype in both irbesartan (p >0.999) and valsartan (p=0.149). There was a trend toward a slightly more pronounced decrease in the daytime HR in the heterozygotes receiving irbesartan by a mean of 1.9 bpm compared to the *CC* homozygotes (p=0.059). The *CT* heterozygotes taking valsartan, were characterized by a less pronounced decrease in the HR by a mean of 1.4 bpm compared to the *TT* homozygotes (p=0.045). Moreover, the minimum drug concentration was not a statistically significant mediator of the effects (p=0.484 and p=0.736, respectively).

Conclusion. When personalizing the AH therapy in the patients of the Moscow region, to optimize the achievement of the target BP, the carriers of the *TT* genotype *C-344T* on the *CYP11B2* gene should be recommend valsartan as the starting therapy of ARBs in the form of the mono- or bicomponent therapy depending on the AH degree.

Keywords: arterial hypertension; aldosterone synthase; *CYP11B2; C-344T* polymorphism

Abbreviations: AH – arterial hypertension; C-344T – genetic polymorphism rs*1799998* of the aldosterone synthase *CYP11B2* gene; ARBs – angiotensin II receptor blockers; BP – blood pressure; DBPM – Daily BP monitoring; HR – heart rate; AHDs – antihypertensive drugs; SNP – single nucleotide polymorphism; GWAS – genome-wide association studies; SBP – systolic blood pressure; DBP – diastolic blood pressure; I/D polymorphism – insertion-deletion polymorphism; RAAS – renin-angiotensin-aldosterone system; ACE – angiotensin-converting enzyme; ECG – electrocardiography; BMI – body mass index; BA – bronchial asthma; AHT – antihypertensive therapy; ADR – adverse drug reaction.

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ОРИГИНАЛЬНАЯ СТАТЬЯ

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Влияние полиморфизма *C-344T* гена альдостерон синтазы на вариабельность антигипертензивной терапии блокаторами рецептора ангиотензина II: открытое рандомизированное контролируемое клиническое исследование

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Эффективность антигипертензивной терапии может быть ассоциирована с генетическими факторами, которые влияют не только на степень повышения артериального давления, но и предопределяют межиндивидуальную вариабельность ответа на антигипертензивное лечение.

Цель. Изучить фармакодинамические показатели эффективности терапии блокаторами рецепторов ангиотензина II в виде монотерапии и в составе комбинированных препаратов у пациентов с артериальной гипертензией (АГ) в зависимости от генетических особенностей пациентов – полиморфизма гена, кодирующего альдостерон синтазу, или *C-344T* полиморфизм.

Материалы и методы. В исследование включено 179 пациентов Московского региона с впервые выявленной АГ 1–2 степени (141 (78,8%) женщина и 38 (21,2%) мужчин) в возрасте от 32 до 69 лет, которые были случайным образом распределены по группам лечения ирбесартаном и валсартаном в виде моно- или комбинированной терапии с гидрохлортиазидом методом простой рандомизации. Через 3 недели фармакотерапии определяли наличие генетического полиморфизма *rs1799998* (*C-344T*) гена альдостерон синтазы *CYP11B2* и определения минимальной равновесной концентрации блокаторов рецептора ангиотензина II (БРА).

Результаты. Гомозиготы *TT* в группе ирбесартана характеризовались более низким уровнем достижения целевых цифр артериального давления (АД) через 3 недели фармакотерапии и более высокой частотой возникновения необходимости интенсификации антигипертензивной терапии по сравнению с генотипами *CT* и *TT*. Среди пациентов, принимавших валсартан, носители генотипа *TT* характеризовались более высокой частотой достижения целевых цифр АД через 3 недели фармакотерапии по сравнению с генотипами *CC* (p <0,001) и *CT* (p=0,084). При этом достижение целевых цифр АД по результатам показателей измерения офисного АД и суточного мониторирования АД (СМАД) на момент окончания исследования не было достоверно взаимосвязано с генотипом *CYP11B2 C-344T* как при назначении ирбесартана (p >0,999), так и валсартана (p=0,149). Выявлена тенденция к несколько более выраженному уменьшению дневной ЧСС у гетерозигот, принимавших ирбесартан, в среднем на 1,9 уд/мин по сравнению с гомозиготами *CC* (p=0,059). Гетерозиготы *CT*, принимавшие валсартан, характеризовались менее выраженным уменьшением ЧСС в среднем на 1,4 уд/мин по сравнению с гомозиготами *TT* (p=0,045). При этом минимальная концентрация препарата не была статистически значимым медиатором эффектов (p=0,484 и p=0,736 соответственно).

Заключение. При персонализации терапии АГ пациентам Московского региона, носителям генотипа *TT* по *C-344T* гена *CYP11B2* для оптимизации достижения целевых цифр АД целесообразно рекомендовать в качестве стартовой терапии БРА валсартан в виде моно- или двухкомпонентной терапии в зависимости от степени АГ.

Ключевые слова: артериальная гипертензия; альдостерон синтаза; *CYP11B2*; *C-344T* полиморфизм

Список сокращений: АГ – артериальная гипертензия; С-344Т – генетический полиморфизм *rs1799998* гена альдостерон синтазы *CYP11B2*; БРА – блокаторы рецептора ангиотензина II; АД – артериальное давление; СМАД – суточное мониторирование АД; ЧСС – частота сердечных сокращений; ЛС – лекарственное средство; АГП – антигипертензивные препараты; SNP – однонуклеотидный полиморфизм; GWAS – полногеномный поиск ассоциаций; САД – систолическое артериальное давление; ДАД – диастолическое артериальное давление; I/D полиморфизм – инсерционно-делеционный (I/D) полиморфизм; РААС – ренин-ангиотензин-альдостероновая система; СКФ – скорость клубочковой фильтрации; АПФ – ангиотензинпревращающий фермент; ЭКГ – электрокардиография; ИМТ – индекс массы тела; БА – бронхиальная астма; АГТ – антигипертензивная терапия; НЛР – нежелательная лекарственная реакция.

INTRODUCTION

The arterial hypertension (AH) is a polygenic inherited disease and one of the major modifiable risk factors for cardiovascular events [1–3]. The prevalence of AH is steadily increasing worldwide. According to different authors' estimates, the number of people suffering from AH is expected to increase by 60% over the next 20 years, which will amount to more than 1.5 billion people [4–8].

The genetic structure that can influence the blood pressure (BP) currently includes more than 30 genes, with rare variants resulting in monogenic forms of

hypertension or hypotension, and more than 1477 single nucleotide polymorphisms (SNPs) associated with the phenotypic effect on BP. The majority of SNPs identified in genome-wide association studies (GWAS) as associated with the BP phenotype, show pleiotropic associations, the study of which will help to understand the underlying biological pathways [9].

Aldosterone is the major mineralocorticoid of the adrenal cortex. It is synthesized from cholesterol in response to an increase in angiotensin II or plasma potassium levels. Aldosterone stimulates a tubule reabsorption of sodium cations, chloride anions, and an excretion of potassium cations, and increases a tissue water-holding capacity, which promotes fluid and sodium transfer from the vascular bed to the tissues. Aldosterone synthesis is carried out under the action of the aldosterone synthase enzyme encoded by the *CYP11B2* gene (cytochrome *P450*, family 11, subfamily B, polypeptide 2) localized on the 8th chromosome at locus 8q21–q22 [10, 11].

About 227 single nucleotide polymorphisms (SNPs) have been identified for the *CYP11B2* gene that may be associated with an increased *CYP11B2* transcription, an increased aldosterone production, and a progression of many cardiovascular diseases, but only a few SNPs have been studied at present. The most widely studied is the *C-344T* polymorphism (*rs id 1799998*; cytosine to the thymidine substitution in the 5′ promoter region of the *CYP11B2* gene, position –344) [12, 13]. This site is the binding site of the steroidogenic transcription factor SF-1, a regulator of the aldosterone synthase gene expression. The *T* allele leads to the increased aldosterone production, which, in turn, is associated with the AH, as well as with myocardial fibrosis and hypertrophy, with the risk of hypertensive complications of pregnancy, with the development of an endothelial dysfunction and cardiovascular complications in patients with a chronic kidney disease [14–16].

Personalized pharmacotherapy of AH based on genetic variations of genes responsible for the function of metabolic enzymes of drugs, the genes that are involved in the pathogenetic mechanisms of the AH development and alter the pharmacodynamic effects of drugs, the genes associated with drug transporters, will improve the effectiveness of the AH pharmacotherapy in patients who regularly receive antihypertensive drugs (AHDs) in accordance with clinical recommendations at the same time not reaching the target values of BP [17–20].

THE AIM of the work was to study pharmacodynamic parameters of the efficacy of therapy with angiotensin II receptor blockers as monotherapy and as a part of combined drugs in patients with AH depending on the genetic features of patients – the gene polymorphism encoding aldosterone synthase, or C-344T polymorphism.

MATERIALS AND METHODS

Study Design

An open randomized controlled clinical study was performed. The study included 179 patients living in the Moscow region with a newly diagnosed 1–2-degree AH. The patients were 141 (78.8%) women and 38 (21.2%) men aged from 32 to 69 years (mean age – 58.2±6.4, the median age – 60 (57–63 years) [21, 22].

Randomization procedure

All the patients included in the study were allocated to groups by a simple randomization (an envelope method).

Eligibility criteria

The patients met the following *inclusion criteria*: the 1–2-degree AH; the age from 18 to 74 years; a signed informed consent of the patient for the participation in the study and a publication of personal medical information.

The *non-inclusion criteria* of patients in the study were: the 3rd degree AH; uncontrolled AH; arterial hypotension; hypersensitivity to irbesartan and valsartan or auxiliary components of the drug; an active liver disease or an increase in the serum transaminase activity more than 3 times; hepatic insufficiency (classes A and B on the Child-Pugh scale); a stage 4–5 chronic kidney disease (glomerular filtration rate less than 30 ml/min/1.73 m^2; creatinine clearance <30 ml/min); decompensated diabetes mellitus; pregnancy and lactation; the age under 18 years and over 75 years; patients with primary hyperaldosteronism, angioedema, including Quincke's edema; during the treatment with drugs affecting renin-angiotensin-aldosterone system (RAAS), including angiotensin-converting enzyme (ACE) inhibitors; a concomitant use of aliskiren and drugs containing aliskiren in patients with diabetes mellitus and/or a moderate or severe renal dysfunction (glomerular filtration rate, GFR) less than 60 ml/min/1.73 m^2 body surface area); a concomitant use of inhibitors with ACE in patients with diabetic nephropathy; galactose intolerance, lactase insufficiency and glucose-galactose malabsorption syndrome; established diagnosis of malignant tumors; diabetes mellitus, lactose intolerance, lactase deficiency and glucose-galactose malabsorption syndrome; an established diagnosis of malignant neoplasm at the time of the inclusion in the study; the need for a continuous intake of non-steroidal anti-inflammatory drugs and/or drugs metabolized by cytochrome *P-450 CYP2C9*, which may affect the effectiveness and safety profile of irbesartan.

The *exclusion criteria:* no patients were excluded during the study [21, 22].

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Conditions and duration of the study

Patients were recruited in the period from July 1, 2021 to August 28, 2022. The search for study participants was carried out in the outpatient treatment and preventive care institutions of Moscow, clinical bases of the Department of Clinical Pharmacology and Propaedeutics of Internal Medicine of Sechenov First Moscow State Medical University (Sechenov University): Mukhin City Clinical Hospital, Hospital for War Veterans No. 3, Central Clinical Hospital of Civil Aviation, State Polyclinic No. 2.

Ethical approval

The study was approved by the Local Ethical Committee of Sechenov First Moscow State Medical University (Sechenov University), Protocol No. 05-21 dated March 10, 2021.

Medical intervention

The program of a clinical and instrumental examination of the patient included was: a collection of patients' complaints, anamnesis (presence of risk factors for the AH development, concomitant diseases), a physical examination, a biochemical blood analysis, an office BP measurement, electrocardiography (ECG) to exclude patients with rhythm disturbances or concomitant heart diseases, echo-CG, daily BP monitoring (DBPM). The BP was measured in both arms using the Korotkoff method after a 10-minute rest of the patient in the sitting position, and was determined as the mean of three measurements taken at 1-minute intervals. DBPM was performed when patients were enrolled in the study and after 3 months of therapy, and the values of the standard daytime and nighttime parameters were evaluated: a mean value, a variability of systolic BP (SBP), diastolic BP (DBP), BP, and heart rate (HR).

Three weeks after the inclusion in the study, the blood of patients was collected to determine the genetic *rs1799998 (C-344T)* polymorphism of the aldosterone synthase *CYP11B2* gene and to determine the minimum equilibrium concentration of ARBs. The office BP measurement was performed at each visit: at the inclusion in the study, at the intermediate stage after 3 weeks and after 3 months of therapy. DBPM was performed in patients at the inclusion in the study and after 3 months of therapy [21, 22].

Methods of outcomes registration

The genetic polymorphism *rs1799998 (C-344T)* of the aldosterone synthase *CYP11B2* gene was determined using the reagent kit for a polymorphism detection in the human genome SNP-screen (Syntol, Russia).

The determination of irbesartan and valsartan concentrations in the blood plasma was performed by HPLC on an Agilent 1290 Infinity II LC coupled with the 6470 Triple Quadrupole LC/MS liquid chromatograph (Agilent Technologies, USA), using standard calibration solutions with concentrations of 2500, 1000, 1000, 500, 250, 250, 100, 50, 25 and 10 ng/mL, trifluoroacetic acid, acetonitrile and Milli-Q purified water for HPLC. The additional equipment included ME54 analytical scales (Mettler Toledo, Sweden), single-channel mechanical pipettes with variable volumes of 100–1000 µL and 20–200 µL (Thermo Scientific Black series, USA), Eppendorf centrifuge (Germany), ZORBAX Eclipse plus C-18 HPLC column, 50×2.1 mm, 1.7 µm for HPLC (Agilent Technologies, USA).

Study groups

All the patients included in the study had not previously received regular antihypertensive therapy (AHT) and were randomly allocated to the irbesartan and valsartan groups by simple randomization (an envelope method). The study participants received ARB (irbesartan and valsartan) in monotherapy or in a combination with hydrochlorthiazide for 3 months. So, 83 patients included in the study, received irbesartan 150 mg once a day, 32 of them were on the irbesartan monotherapy, and 51 patients received the combination therapy: irbesartan 150 mg+hydrochlorthiazide 12.5 mg. 96 patients were prescribed valsartan, 8 of them received the valsartan 80 mg monotherapy once daily, and 88 patients received the valsartan 80 mg+hydrochlorthiazide 12.5 mg combination therapy. When the target BP numbers were achieved after 3 weeks of therapy (<140/90 mm Hg, if well tolerated <130/80 mm Hg, but not <120/70 mm Hg), the patients continued to adhere to their therapy for 3 months of treatment. In case of an insufficient BP control, the intensification of therapy was performed by doubling the dose of irbesartan or valsartan as part of the mono- or combination therapy.

Statistical processing

The sample size was not pre-calculated. The statistical analysis and visualization of the obtained data were performed using the R 4.3.1 statistical computing environment (R Foundation for Statistical Computing, Vienna, Austria).

Descriptive statistics for quantitative variables without a pronounced asymmetry of conditional sampling distributions are presented as a mean (±standard deviation, SD), for quantitative variables with a pronounced asymmetry (absolute values of the asymmetry coefficient >1.96) – as a median [Q1; Q3]. Descriptive statistics for qualitative variables are presented as a number of observations (a relative frequency). The Fisher's exact test was used to compare

the groups with respect to qualitative variables (including the Holm correction for multiple pairwise comparisons). The Welch's *t*-test and Mann–Whitney test were used to compare two independent groups with respect to quantitative variables, and the Kraskell–Wallis test and Dunn's test with the Holm correction for pairwise post-hoc comparisons were used to compare three groups. The differences were considered statistically significant at p <0.05.

The chi-square test (χ^2) was used to analyze the correspondence of the empirical distribution of genotypes to the theoretical one defined by the Hardy–Weinberg equilibrium.

For a correlation analysis, the Spearman's rank correlation coefficient ρ with corresponding 95% confidence intervals (95% CI) was used, and the regression coefficients (with a corresponding 95% CI) in single-factor regression models were estimated if there was a statistically significant correlation between quantitative indicators. To assess the strength and statistical significance of the association of quantitative predictors with binary outcomes, single-factor logistic regression models with coefficients estimated with the Firth (1993) correction for rare outcomes were used.

In the comparative analysis of genotype effects with changes in SBP, DBP, and HR, linear regression models were used with the inclusion of an interaction term between the genotype and drug used and robust standard errors of the regression coefficients. To assess the relative contribution of the drug concentration as a mediator of the identified genotype effects, two linear regression models were constructed: a two-factor outcome model including the genotype and the concentration and a single-factor genotype-dependent concentration model, which had been used to estimate the total and partial genotype effects and the ratio of coefficients (the sum of coefficients) to calculate the proportion of the genotype effect mediated by the concentration (the standard error was estimated using a nonparametric analysis). The association was considered statistically significant at p <0.05.

RESULTS AND DISCUSSION

Characteristics of study groups

Table 1 shows the demographic and anamnestic characteristics of the patient groups.

In the comparative analysis, it was found out that valsartan was statistically significantly more often prescribed to male patients (p <0.001). The patients were comparable in age (p=0.24). The patients receiving valsartan also had a statistically significantly higher BMI and were more likely to have a grade 3 obesity (p <0.001). In addition, the patients in this group were statistically significantly more likely to have bronchial asthma (BA; p=0.012) and statistically significantly less likely to have a history of Crohn's disease (p=0.044).

Main study result

All patients were genotyped according to the *C-344T* polymorphism of the aldosterone synthase *CYP11B2* gene. According to the data obtained, the frequency of the polymorphic allele *T* carriage by the polymorphism *C-344T* of the aldosterone synthase *CYP11B2* gene was 192 (53,6%), while 51 patients (28,5%) were homozygotes for the mutant allele and carriers of the *TT* genotype, and 90 (50,3%) patients were heterozygous representatives of the *CT* genotype. There were no statistically significant deviations of the observed frequency of genotypes for the *C-344T* polymorphism of the *CYP11B2* aldosterone synthase gene from the theoretical one determined by the Hardy-Weinberg equilibrium (χ^2=0.003, p=0.96).

Values of the minimum equilibrium irbesartan concentration in patients with the *CC* genotype by the *C-344T* polymorphism of the aldosterone synthase *CYP11B2* gene were determined at the level of 1788 (1633-2341) ng/mL, with the *CT* genotype – 1909 (1707–2346) ng/mL, with the *TT* genotype – 2476 (1969–2672) ng/mL. The mean values of the minimal equilibrium concentration of valsartan in patients with the *CC* genotype by the *C-344T* polymorphism of the aldosterone synthase *CYP11B2* gene were determined at the level of 1380 (1172–1568) ng/mL, with the *CT* genotype – at 1095 (740–1428) ng/mL, with the *TT* genotype – at 688 (519–1562) ng/mL.

Table 2 summarizes the results of SBP, DBP and HR dynamics in patients with different genotypes for the *C-344T* polymorphism of the aldosterone synthase *CYP11B2* gene.

The *TT* homozygotes at the *C-344T* polymorphic locus of the *CYP11B2* gene taking irbersartan, were characterized by a statistically significantly less pronounced reduction in the office SBP after 3 weeks of therapy by a mean of 5.5 [95% CI: 0.2; 10.9] mmHg (p=0.042); this effect was not associated with the concentration magnitude (p=0.708).

At the time of the interim phase of the study, the heterozygotes taking valsartan had a statistically significantly greater mean reduction in the SBP of 15.7 [95% CI: –21.9; –9.5] mmHg compared to the *CC* homozygotes (p <0.001) and 7.5 [95% CI: –13.4; –1.6] mmHg with the *TT* homozygotes (p=0.009). The *TT* homozygotes were characterized by a more pronounced reduction in the SBP by a mean of 8.2 [95% CI: –15; –1.4] mmHg compared to the *CC* homozygotes (p=0.014); this effect was not associated with the concentration value (p=0.538).

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Table 1 – Demographic and anamnestic characteristics of patient groups

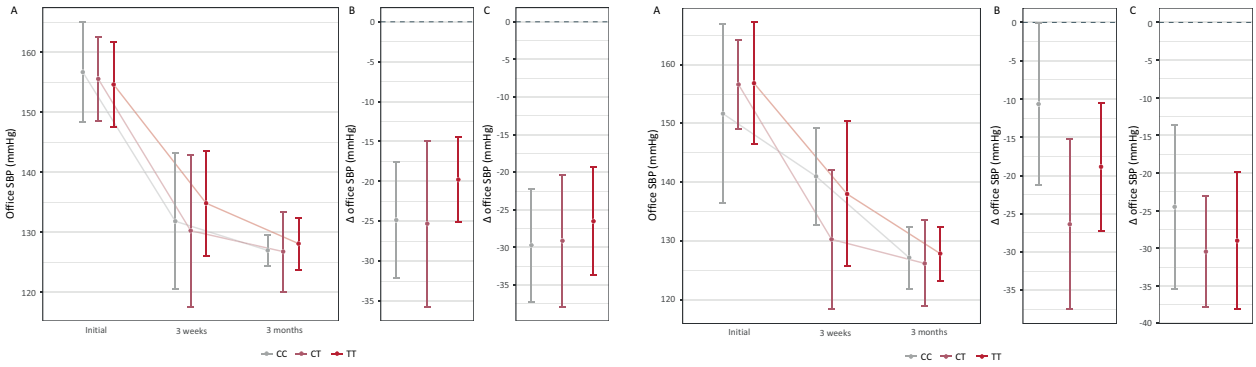
Characteristics		Irbesartan (*n*=83)	Valsartan (*n*=96)	*p*
Gender, *n* (%)		–	–	<0,001
	female	53 (63.9%)	88 (91.7%)	–
	male	30 (36.1%)	8 (8.3%)	–
Age, years		57 (±7.5)	59.3 (±5.1)	0.24
BMI, kg/m^2		29.4 (±5.4)	33.4 (±6.8)	<0.001
Obesity		–	–	<0.001
None		38 (45.8%)	44 (45.8%)	–
	Degree 1	29 (34.9%)	16 (16.7%)	–
	Degree 2	16 (19.3%)	20 (20.8%)	–
	Degree 3	0 (0%)	16 (16.7%)	–
Chronic gastritis, *n* (%)		10 (12%)	16 (17%)	0.382
Chronic tonsillitis, *n* (%)		7 (8.4%)	4 (4.2%)	0.236
Bronchial asthma, *n* (%)		2 (2.4%)	12 (13%)	0.012
Varicose veins of lower limbs, *n* (%)		8 (9.6%)	4 (4.2%)	0.144
Migraine, *n* (%)		2 (2.4%)	4 (4.2%)	0.687
Crohn's disease, n (%)		4 (4.8%)	0 (0%)	0.044
Psoriasis, *n* (%)		2 (2.4%)	0 (0%)	0.214
Osteochondrosis, *n* (%)		13 (16%)	12 (13%)	0.543

Note: BMI – body mass index; BA – bronchial asthma.

Table 2 – SBP, DBP and HR in patients with different genotypes for the C-344T polymorphism of the CYP11B2 gene in the irbesartan and valsartan patient groups

Characteristics	Irbesartan				Valsartan			
	CC	*CT*	*TT*	*p*	*CC*	*CT*	*TT*	*p*
Δ office SBP after 3 weeks	–24.9 (±7.3)	–25.3 (±10.4)	–19.8 (±5.3)	**0.026**	–10.7 (±10.5)	–26.4 (±11.1)	–18.9 (±8.4)	**<0.001**
Δ office SBP at the end of the study	–29.7 (±7.5)	–29.1 (±8.8)	–26.5 (±7.2)	0.287	–24.5 (±10.9)	–30.5 (±7.3)	–29 (±9.1)	**0.039**
Δ office DBP after 3 weeks	–18.3 (±7.6)	–20.2 (±7.9)	–14.6 (±9.3)	**0.071**	–10.8 (±14.5)	–16.1 (±12.2)	–13.9 (±7.7)	**0.073**
Δ office DBP at the end of the study	–23.9 (±9.8)	–25.4 (±7.3)	–23 (±8.8)	0.583	–23.3 (±10.3)	–20.5 (±6.8)	–24.3 (±9.6)	0.271
Δ office HR after 3 weeks	–1.9 (±4.2)	–3.4 (±3.3)	–2.6 (±3.6)	0.412	–4.2 (±4.1)	–1.6 (±7)	–5.7 (±4.4)	**0.06**
Δ office HR at the end of the study	–2.3 (±5.2)	–3.6 (±3.6)	–2.7 (±4.6)	0.819	–5.5 (±5)	–4.5 (±4.1)	–5.7 (±4.3)	0.525
Achievement of target BP after 3 weeks	9/14 (64.3%)	30/46 (65.2%)	12/23 (52.2%)	0.53	4/24 (16.7%)	20/44 (45.5%)	20/28 (71.4%)	**<0.001**
Dose increase (AHT intensification)	5/14 (35.7%)	13/46 (28.3%)	11/23 (47.8%)	0.262	20/24 (83.3%)	20/44 (45.5%)	16/28 (57.1%)	**0.009**
Δ mean daytime SBP	–27.6 (±6.7)	–28.5 (±9.5)	–27 (±6.5)	0.879	–31 (±6.2)	–32 (±7.7)	–27 (±4.4)	**0.035**
Δ mean daytime DBP	–29.9 (±5.1)	–30.3 (±6.2)	–31.1 (±5.9)	0.706	–30 (±6.6)	–27.2 (±5.6)	–29.9 (±5.8)	0.174
Δ mean daytime HR	–0.4 (±2.4)	–2.3 (±2.2)	–1.3 (±3.4)	**0.072**	–3 (±2.1)	–1.9 (±2.4)	–3.3 (±2.5)	**0.042**
Δ mean nighttime SBP	–17.9 (±5.5)	–17.4 (±9.4)	–15 (±6.9)	0.359	–19.7 (±6.8)	–17.1 (±7.2)	–17.4 (±8.7)	0.461
Δ mean nighttime DBP	–24.9 (±5.3)	–25.8 (±5.6)	–25.1 (±5.9)	0.848	–27.3 (±6.5)	–24.5 (±6.2)	–28.7 (±3.6)	**<0.001**
Δ mean nighttime HR	–0.9 (±4.7)	–2.2 (±3.6)	–2.4 (±3.8)	0.742	–3.8 (±3)	–4.1 (±4.9)	–4.7 (±4.7)	0.408
Δ daytime SBP variability	–5.5 (±3.5)	–6.1 (±3.5)	–5.9 (±3.7)	0.419	–8.2 (±0.4)	–8.3 (±0.4)	–8.4 (±0.6)	0.626
Δ daytime DBP variability	–2.8 (±2.2)	–2.6 (±1.9)	–2.5 (±1.9)	0.756	–4.3 (±0.5)	–3.5 (±0.7)	–4 (±0.5)	**<0.001**
Δ nighttime SBP variability	–1.8 (±1.7)	–2 (±1.5)	–1.7 (±1.2)	0.713	–2.7 (±1)	–3 (±0.6)	–2.7 (±1.1)	0.196
Δ nighttime DBP variability	–0.8 (±0.7)	–0.7 (±0.7)	–0.7 (±0.8)	0.775	–1 (±0.4)	–1.3 (±0.6)	–1.4 (±0.7)	0.2
Achievement of target BP at the end of the study	14/14 (100%)	43/44 (97.7%)	23/23 (100%)	>0.999	24/24 (100%)	40/44 (90.9%)	28/28 (100%)	0.149
ADR (arterial hypotension)	0/14 (0%)	3/46 (6.5%)	0/23 (0%)	0.741	0/24 (0%)	4/44 (9.1%)	0/28 (0%)	0.149

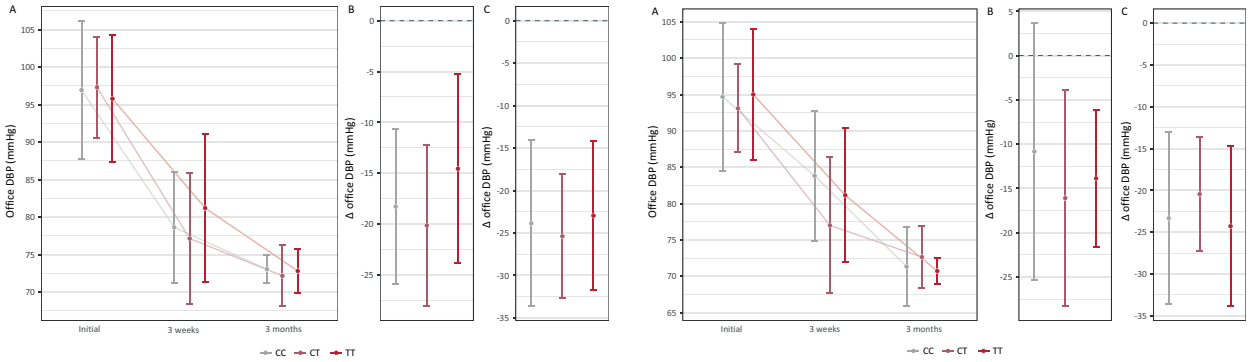
Note: * Statistically significant values are highlighted in bold at p <0.05. SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; BP – blood pressure; AHT – antihypertensive therapy; ADR – adverse drug reaction.



A **B**

Figure 1 – Comparative analysis of the office SBP dynamics in patients with different genotypes for the *C-344T* polymorphism of the *CYP11B2* gene in the irbesartan and valsartan patient groups

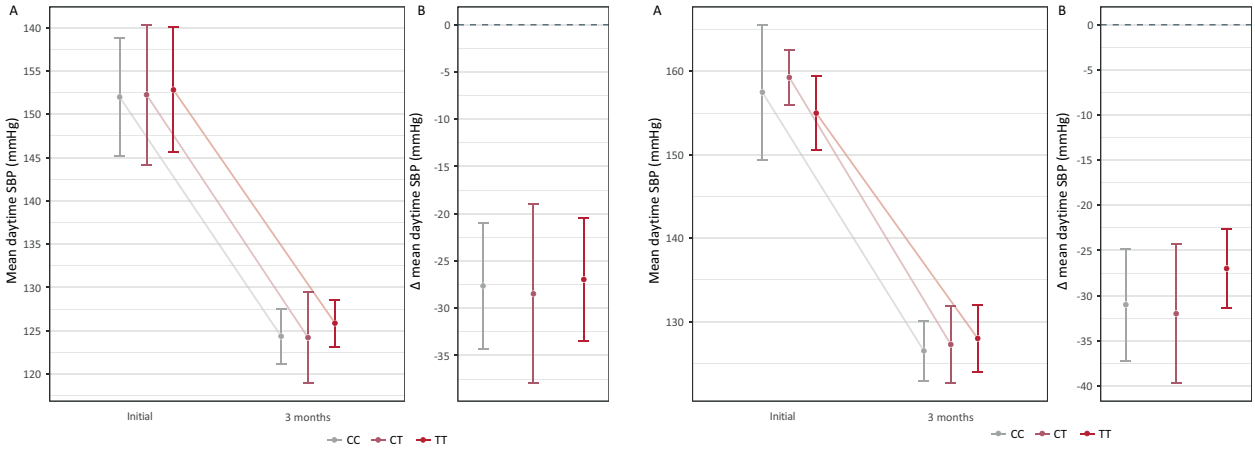
Note: A – irbesartan group; B – valsartan group; SBP – systolic blood pressure.



A **B**

Figure 2 – Comparative analysis of the office DBP dynamics in patients with different genotypes for the *C-344T* polymorphism of the *CYP11B2* gene in the irbesartan and valsartan patient groups

Note: A – irbesartan group; B – valsartan group; DBP – diastolic blood pressure.



A **B**

Figure 3 – Comparative analysis of the dynamics of the mean daytime SBP in patients with different genotypes for the *C-344T* polymorphism of the *CYP11B2* gene in the irbesartan and valsartan patient groups

Note: A – irbesartan group; B – valsartan group; SBP – systolic blood pressure.

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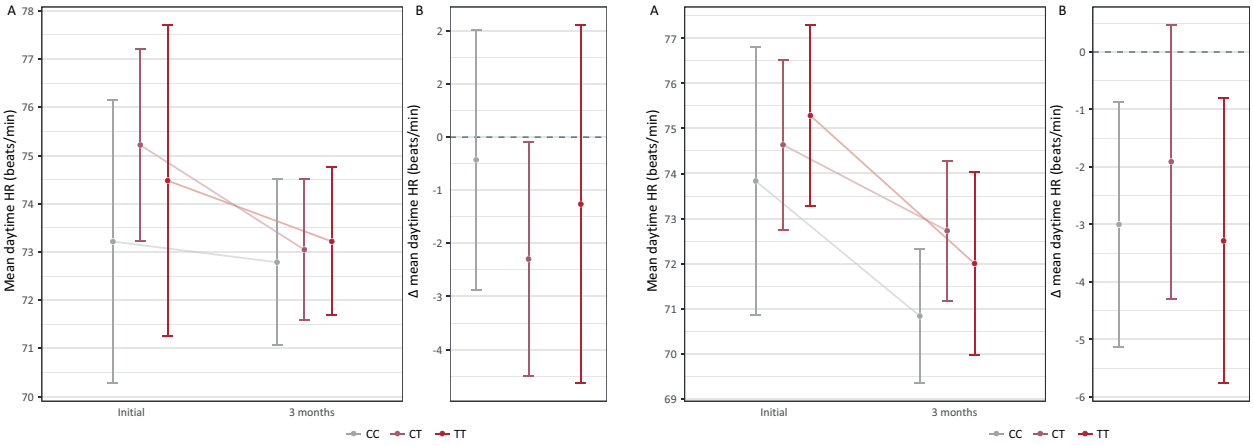

Figure 4 – Comparative analysis of the dynamics of mean daily HR in patients with different genotypes for the *C-344T* polymorphism of the *CYP11B2* gene in the irbesartan and valsartan patient groups
Note: A – irbesartan group; B – valsartan group; HR – heart rate.

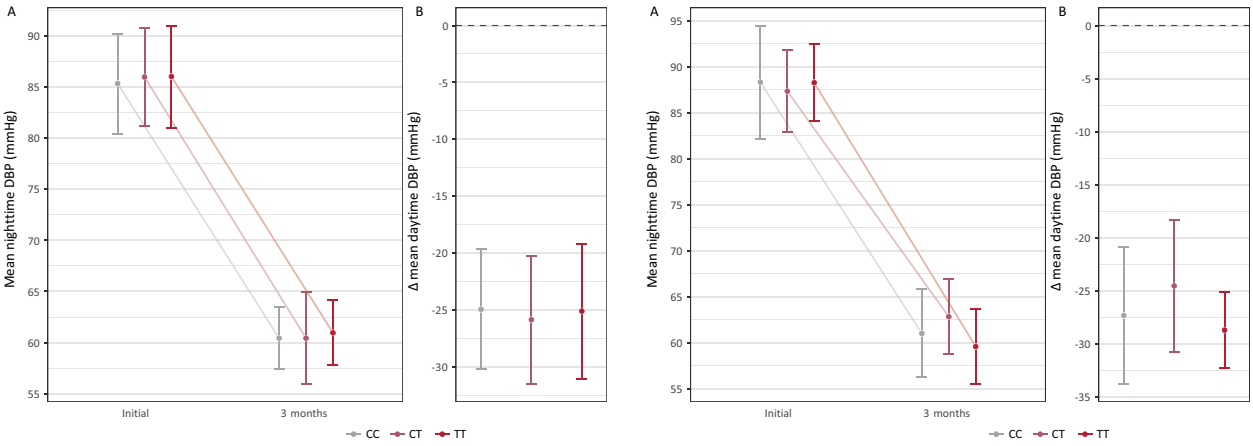

Figure 5 – Comparative analysis of mean nighttime DBP dynamics in patients with different genotypes for the *C-344T* polymorphism of the *CYP11B2* gene in the irbesartan and valsartan patient groups
Note: A – irbesartan group; B – valsartan group; DBP – diastolic blood pressure.

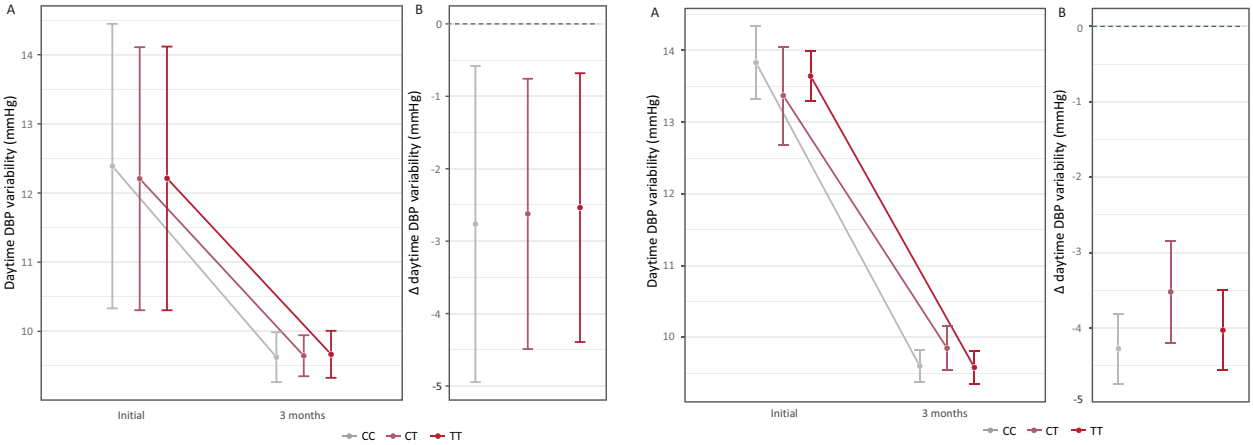

Figure 6 – Comparative analysis of the dynamics of daytime DBP variability in patients with different genotypes for the *C-344T* polymorphism of the *CYP11B2* gene in irbesartan and valsartan patient groups
Note: A – irbesartan group; B – valsartan group; DBP – diastolic blood pressure.

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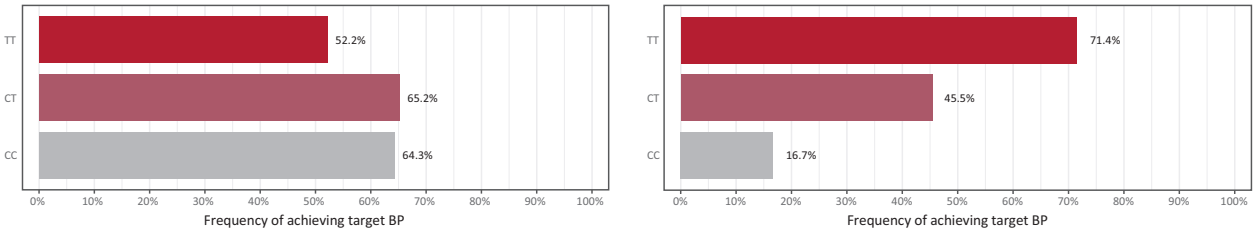

Figure 7 – Comparative analysis of the frequency of achieving the target BP in patients with different genotypes for the *C-344T* polymorphism of the *CYP11B2* gene in irbesartan and valsartan patient groups

Note: A – irbesartan group; B – valsartan group; BP – blood presure.

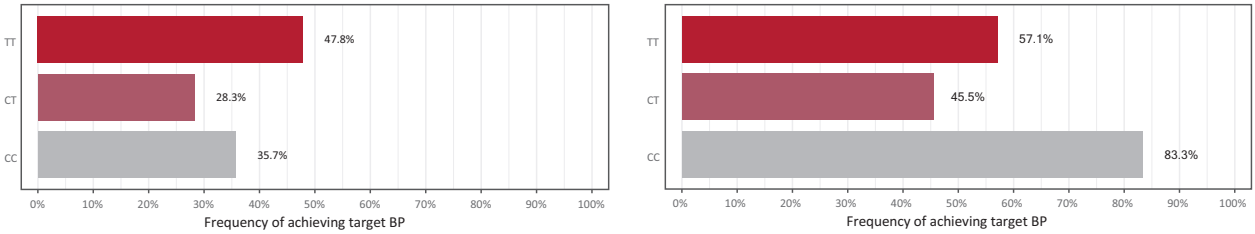

Figure 8 – Comparative analysis of the necessity incidence to intensify antihypertensive therapy in patients with different genotypes for the *C-344T* polymorphism of the *CYP11B2* gene in the irbesartan and valsartan patient groups

Note: A – irbesartan group; B – valsartan group; BP – blood presure.

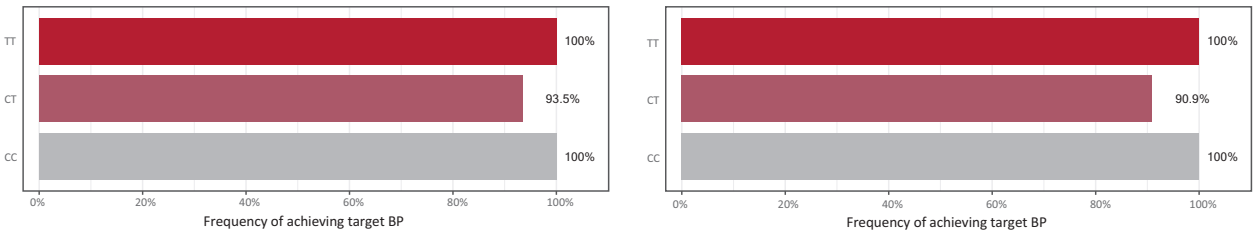

Figure 9 – Comparative analysis of the frequency of reaching the target BP at the end of the study in patients with different genotypes for the *C-344T* polymorphism of the *CYP11B2* gene in the irbesartan and valsartan patient groups

Note: A – irbesartan group; B – valsartan group; BP – blood presure.

There was no statistically significant association of the *CYP11B2 C-344T* genotype with the effect of irbersartan on the office SBP at the end of the study (p=0.287). The *TT* heterozygotes and homozygotes taking valsartan were characterized by a more pronounced reduction in the office SBP at the end of the study by a mean of 6 [95% CI: –11.3; –0.6] mmHg (p=0.026) and 4.5 [95% CI: –10.4; 1.4] mmHg (p=0.167) compared to the CC homozygotes, this effect was not associated with the concentration magnitude (p=0.574). The summarized data is shown in Figure 1.

At the interim assessment, there was a statistically significant less pronounced mean 5.6 [95% CI: 0.5; 10.6] mmHg reduction in the office DBP among the *TT* homozygotes receiving irbesartan compared to the *CT* heterozygotes (p=0.027); the effect was not associated with the magnitude of the equilibrium drug concentration (p=0.5). There was no statistically significant association of the drug effect on the office DBP with the genotype (p=0.583 and p=0.271, respectively; Fig. 2).

There were no statistically significant differences regarding the effect of irbesartan on the mean daytime SBP depending on the *CYP11B2 C-344T* genotype *(p=0.879).* The *TT* homozygotes receiving valsartan were characterized by a less pronounced reduction in the daytime SBP by a mean of 4 [95% CI: –0.3; 8.3] mmHg compared to the *CC* homozygotes (p=0.075) and 5 [95% CI: 1.3; 8.7] mmHg compared to the heterozygotes (p=0.006). This effect was not associated with the equilibrium drug concentration value (p=0.868; Fig. 3).

There was a trend towards a slightly more

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pronounced reduction in the daytime HR in the heterozygotes at the *CYP11B2 C-344T* locus taking irbesartan by a mean of 1.9 [95% CI: –3.8; 0.1] bpm compared to the *CC* homozygotes (p=0.059*),* this effect was not associated with the equilibrium drug concentration value (p=0.484*).* The *CT* heterozygotes taking valsartan were characterized by a less pronounced reduction in the HR by a mean of 1.4 [95% CI: 0; 2.7] bpm compared to the *TT* homozygotes (p=0.045)*,* with the drug concentration also not being a statistically significant mediator of the effect (p=0.736; Fig. 4).

There was no statistically significant association of the irbesartan effect on the mean nighttime DBP with the genotype at the *CYP11B2 C-344T* locus (p=0.848). The *TT* homozygotes taking valsartan were characterized by a more pronounced reduction in the nighttime DBP by a mean of 4.2 [95% CI: –7.4; –0.9] mmHg compared to the heterozygotes (p=0.008). This effect was not associated with the value of the equilibrium drug concentration (p=0.7; Fig. 5).

Among the patients taking irbesartan, no statistically significant association of the daytime BP variability with the genotype at the *CYP11B2 C-344T* locus was found (p=0.756). The heterozygotes taking valsartan were characterized by a statistically significant smaller reduction in the daytime DBP variability by a mean of 0.8 [95% CI: 0.4; 1.1 mmHg compared to the *CC* homozygotes (p <0.001) and 0.5 [95% CI: 0.1; 0.9] mmHg compared to the *TT* homozygotes (p=*0.003*). This effect was not associated with the equilibrium value of the drug concentration (p=0.642; Fig. 6).

There was no statistically significant association of the frequency of reaching the target BP at the interim assessment and the need for a dose increase in patients taking irbesartan (p=0.53 and p=0.262, respectively). Among the patients taking valsartan, the *TT* genotype was characterized by a higher frequency of achieving the target BP at the interim evaluation compared to the *CC* (p <0.001) and *CT* (p=0.084) genotypes. The *CC* genotype was also characterized by a higher frequency compared to heterozygotes (p=0.059). The *CC* genotype was also characterized by the greatest need for the intensification of the AHT (p=0.009). The achievement of the target BP at the end of the study was not statistically significantly associated with the *CYP11B2 C-344T* genotype when irbesartan (p >0.999) and valsartan (p=0.149) were used (Fig. 7–9).

DISCUSSION

When studying the genotype frequency distribution for the genetic polymorphism *C-344T* of the aldosterone synthase *CYP11B2* gene, which catalyzes the reaction of the aldosterone synthesis, the following results were obtained: the *CC* genotype was determined in 38 patients, corresponding to 21.2% of the sample, the *CT* genotype – in 90 (50.3%) patients and the *TT* genotype – in 51 (28.5%). The frequency of the *C* allele was 166 (46.4%) and the frequency of the *T* allele was 192 (53.6%).

In the study by Ji X. et al. [23], conducted in China, which included 345 patients with AH and 157 control subjects, the frequency of genotypes by the genetic polymorphism *C-344T* of the aldosterone synthase *CYP11B2* gene was analyzed. The following results were obtained: the frequency of the *CC* genotype occurrence among the patients suffering from the AH was 15.1%, from the *CT* genotype – 51.9%, from the *TT* genotype – 33%. The distribution of the genotypes in the control group among the healthy individuals was as follows: 8.3% of the people carried the *CC* genotype, 46.8% – the *CT* genotype, and 44.9% – the *TT* genotype. Thus, the frequency of the *C* allele was significantly higher in the patients with the AH compared with the controls (p <0.05) in the Chinese population. Thus, the distribution of genotype frequencies for the *C-344T* genetic polymorphism of the aldosterone synthase *CYP11B2* gene among 179 patients with newly diagnosed AH of the 1–2-degree in the Moscow region corresponds to the distribution of the genotypes in the Chinese population.

In the controlled study by Li X. et al. [10], 2115 people, residents of Tibet and northwest China, participated. The authors determined a direct correlation in the female population between the *C-344T* polymorphism of the *CYP11B2* gene and the development of the essential hypertension (EH) – the frequencies of the *CC* and *CT* genotypes and *C* allele in the EH group were higher than in the control group (p <0.05).

In the study by Yakimenko O. et al [11], the aim of which was to study the prevalence of the *C-344T* polymorphism and the distribution of the aldosterone synthase (*CYP11B2*) gene genotypes, to analyze the associations of the left ventricular hypertrophy (LVH) with the aldosterone synthase genotypes in young age patients with AH, the authors found that the *TT*, *CT* genotypes of the *C-344T* polymorphism of the aldosterone synthase gene were associated with higher blood aldosterone concentrations and higher stages of LVH in young patients with AH.

In the study by Ji X. et al. [23], performed in China, among 502 examined patients, the AH was detected in 34. The frequency of the *CC* and *CT* genotypes by the *C-344T* polymorphism of the *CYP11B2* gene, as well as the frequency of the *C*-allele, was significantly higher in patients with the AH compared to patients without the AH (p <0.05). In the prospective part of the study, 98 patients with the AH received the valsartan therapy for 4 weeks. The reduction of the SBP, DBP, as well as the SBP, DBP parameters obtained during a 24-hour BP monitoring in the group with the *CC* and *CT* genotypes, was significantly more pronounced than in the group with the *TT* genotype (p <0.05). The data obtained show that when assessing the effectiveness of AHT at the intermediate stage, the patients in the valsartan group, heterozygous for the *C-344T* polymorphism of the *CYP11B2* gene, reduced the office SBP more intensively by 15.7 [95% CI: –21.9; –9.5] mmHg. Hg compared with the *CC* genotype carriers (p <0.001) and by 7.5 [95% CI: –13.4; –1.6] mmHg compared with the *TT*

homozygotes (p=0.009). Herewith, the *TT* genotype carriers showed a significantly more intense reduction of 8.2 [95% CI: –15; –1.4] mmHg compared to the *CC* genotype carriers (p=0.014). However, when analyzing associations based on the results of the conducted DBPM, when included in the study and after 3 months of AHT, *TT* homozygotes for *C-344T* of the *CYP11B2* gene on average by 4 [95% CI: –0.3; 8.3] mmHg did not significantly reduce the average daily SBP compared with *CC* homozygotes (p=0.075) and by 5 [95% CI: 1.3; 8.7] mmHg compared with heterozygotes (p=0.006). The *TT* homozygotes for C-344T of the CYP11B2 gene had a mean 4.2 [95% CI: –7.4; –0.9] mmHg less pronounced reduction in the mean nighttime DBP compared to the heterozygotes (p=0.008). The obtained data may indicate a functional cumulation of drugs and the stabilization of the pharmacodynamic effect.

After 3 months of the irbesartan treatment, the SILVHIA study (The Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol) [24] showed a more pronounced decrease in the SBP compared to the patients with the *CC* and *TT* genotypes, in the patients with the *TT* genotype by the *C-344T* polymorphism of the *CYP11B2* gene. The authors' findings indicate, when assessed for the effectiveness 3 weeks after prescribed AHT, the patients who received the irbesartan therapy, the *TT* homozygotes for the *C-344T* of the *CYP11B2* gene, were statistically significantly less likely to reduce both the office SBP by 5.5 [95% CI: 0.2; 10.9] mmHg, and the office DBP by 5.6 [95% CI: 0.5; 10.6] mmHg compared with the heterozygotes (p=0.042 and p=0.027, respectively). In the group of patients taking irbesartan, no statistically significant DMBP results were obtained.

In the prospective study by Ortlepp J.R. et al. [25], the patients with the elevated DBP (>95 mmHg) received candesartan in high (16 mg) or low (8 mg) doses in addition to standard medications. Genotyping was performed in 116 patients, and the genotypes of the *CYP11B2* promoter polymorphism significantly predicted a positive response to the treatment: with the genotype *CC*, 67% of patients achieved a reduction in the DBP <85 mmHg, with *TC* – 34% and with *TT* – 21%; p=0.005).

Kurbanova D.R. et al. [26] studied the influence of the *I/D* polymorphism of the *ACE* gene, the *M235T* polymorphism of the *AGT* gene, the *A1166C* polymorphism of the *AGTR1* gene, the *C-344T* polymorphism of the *CYP11B2* gene on the effectiveness of the eprosartan therapy in 48 Uzbek men with AH. The study did not reveal a significant dependence of antihypertensive effectiveness of eprosartan on the carriage of the studied polymorphic genes. However, this may be due to the insufficient sample size.

Thus, a limited number of studies have been performed on the effect of the *C-344T* polymorphism of the *CYP11B2* gene on the effectiveness of AHT, and the results of these studies remain inconsistent.

Study limitations

This study focuses on the influence of a single polymorphism of a candidate gene responsible for the synthesis of aldosterone synthase, the enzyme that catalyzes the synthesis of aldosterone, on the risk of developing the AH and the effectiveness of AHDs. However, the risk of the AH and/or AHDs development may also be influenced by the polymorphisms in the genes involved in the AHDs metabolism, responsible for a certain link of RAAS, involved in pathogenetic mechanisms of the AH development and influencing pharmacodynamic effects of drugs, modifications of mechanical interactions between drugs and genes, as well as polymorphisms in genes related to drug transporters, which requires a further study. This study is also limited by the sample size, region and randomization method.

CONCLUSION

When personalizing the AH therapy in patients of the Moscow region, the carriers of the *TT* genotype *C-344T* of the *CYP11B2* gene, it is reasonable to recommend valsartan as a starting therapy of ARBs in the form of mono- or bicomponent therapy depending on the AH degree.

In this study, a single polymorphism responsible for a particular RAAS link and influencing the risk of the AH development and the response to the ARBs therapy, were analyzed. Herewith, the response to the AHT also depends on the genes, which are involved in pathogenetic mechanisms of the AH development, and modify pharmacodynamic effects of drugs, modify a mechanical interaction between drugs and genes, as well as polymorphisms in the genes related to drug transporters, which determines the need for a further study of the influence of polymorphisms in the panel of candidate genes.

FINDING

This study had no financial support from outside organizations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Ekaterina V. Rebrova – collection and processing of materials, writing the text; Evgenia V. Shikh, Natalia B. Lazareva – collection and processing of materials, editing the text of the article.
All the authors confirm their authorship compliance with the ICMJE international criteria (all authors made a significant contribution to the conceptualization, research and preparation of the article, read and approved the final version before publication).

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