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Effect of insertion/deletion polymorphism of angiotensin-converting enzyme gene on efficacy of antihypertensive therapy with angiotensin II receptor blockers

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The efficacy of the antihypertensive therapy may be related to genetic factors that can influence not only the degree of the blood pressure (BP) elevation but also contribute to the interindividual variability of response to the antihypertensive treatment.

The aim of the work was to study pharmacodynamic parameters of the therapy efficacy with angiotensin II receptor blockers in the form of monotherapy and as part of combined drugs in patients with the arterial hypertension depending on the genetic features of patients – polymorphism of the gene encoding angiotensin-converting enzyme, or I/D-polymorphism.

Materials and methods. The study included 179 patients of the Moscow region with a first-diagnosed arterial hypertension (AH) of 1–2 degree, including 141 (78.8%) women and 38 (21.2%) men aged from 32 to 69 years. By a simple randomization method, the patients were randomly allocated into groups receiving irbesartan and valsartan as mono- or combination therapy with hydrochlorthiazide. After 3 weeks of this pharmacotherapy, the presence of rs4646994 Alu Ins / Del genetic polymorphism of the angiotensin-converting enzyme (ACE) gene and the minimum equilibrium concentration of angiotensin II receptor blockers (ARBs) were determined.

Results. The patients treated with irbesartan, the D/D genotype carriers, were significantly less likely to reach the target BP and more likely to require a pharmacotherapy intensification compared to I/D heterozygotes (p=0.042 and p=0.058, respectively) and I/I homozygotes (p=0.011 and p=0.011, respectively). The patients treated with valsartan, the D/D genotype carriers, significantly more often reached the target BP and significantly less often required a pharmacotherapy intensification than the I/D genotype carriers (p=0.05 and p=0.05, respectively). Herewith, at the end of the study, according to the results of the office BP measurements and daily BP monitoring, the target BP achievement was not significantly correlated with the I/D polymorphism of the ACE gene.

Conclusion. When personalizing the AH therapy in patients of the Moscow region, the genotype I/I carriers by I/D polymorphism of the ACE gene, can be recommended irbesartan in the form of mono- or bicomponent therapy as a starting therapy of ARBs; the D/D genotype carriers can be recommended valsartan. A more pronounced decrease in the daytime systolic BP (SBP), the daytime diastolic BP (DBP) and the nighttime SBP variabilities in the valsartan group of patients, the D allele carriers may indicate a more persistent effect of the antihypertensive therapy.

Keywords: arterial hypertension; angiotensin-converting enzyme; ACE; ACE; I/D polymorphism

Abbreviations: AH – arterial hypertension; AHDs – antihypertensive drugs; BP – blood pressure; I/D polymorphism – insertion/deletion (I/D) polymorphism; ACE – angiotensin-converting enzyme; RAAS – renin-angiotensin-aldosterone system; SBP – systolic blood pressure; DBP – daytime diastolic blood pressure; HR – heart rate; DBPM – daily blood pressure monitoring; ARBs – angiotensin II receptor blockers.

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Влияние инсерционно-делеционного полиморфизма гена ангиотензинпревращающего фермента на эффективность антигипертензивной терапии блокаторов рецептора ангиотензина II

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Эффективность антигипертензивной терапии может быть связана с генетическими факторами, которые могут влиять не только на степень повышения артериального давления (АД), но и способствовать межиндивидуальной вариабельности 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 в зависимости от генетических особенностей пациентов – полиморфизма гена, кодирующего ангиотензинпревращающий фермент или I/D-полиморфизма.

Материалы и методы. В исследование включено 179 пациентов Московского региона с впервые выявленной артериальной гипертензией (АГ) 1–2 степени, среди которых 141 (78,8%) женщины и 38 (21,2%) мужчины в возрасте от 32 до 69 лет. Пациенты случайным образом были распределены по группам, принимавшим ирбесартан и валсартан в виде моно- или комбинированной терапии с гидрохлортиазидом методом простой рандомизации. Через 3 недели фармакотерапии определяли наличие генетического полиморфизма rs4646994 Alu Ins / Del гена ангиотензинпревращающего фермента ACE и минимальную равновесную концентрацию блокаторов рецепторов ангиотензина II (БРА).

Результаты. Пациенты, получавшие терапию ирбесартаном, носители генотипа D/D достоверно реже достигали целевых цифр АД и им чаще требовалась интенсификация фармакотерапии по сравнению с гетерозиготами I/D (p=0,042 и p=0,058 соответственно) и гомозиготами I/I (p=0,011 и p=0,011 соответственно). Пациенты, получавшие терапию валсартаном, носители генотипа D/D достоверно чаще достигали целевых цифр АД и достоверно реже требовалась интенсификация фармакотерапии, чем носителям I/D генотипа (p=0,05 и p=0,05 соответственно). При этом достижение целевых цифр АД по результатам показателей измерения офисного АД и суточного мониторирования АД на момент окончания исследования не было достоверно взаимосвязано с I/D полиморфизмом гена ACE.

Заключение. При персонализации терапии АГ пациентам Московского региона, носителям генотипа I/I по I/D полиморфизму гена ACE, можно рекомендовать в качестве стартовой терапии БРА ирбесартан в виде моно- или двухкомпонентной терапии; носителям генотипа D/D может быть рекомендован валсартан. Более выраженное снижение показателей вариабельности систолического АД (САД) дневного, диастолического АД (ДАД) дневного и САД ночного у пациентов группы валсартана, носителей D-аллели может свидетельствовать о более стойком эффекте антигипертензивной терапии.

Ключевые слова: артериальная гипертензия; ангиотензинпревращающий фермент; ACE; АПФ; I/D полиморфизм

Список сокращений: АГ – артериальная гипертензия; ЛС – лекарственное средство; АГП – антигипертензивные препараты; АД – артериальное давление; I/D полиморфизм – инсерционно-делеционный (I/D) полиморфизм; АПФ – ангиотензинпревращающий фермент; РААС – ренин-ангиотензин-альдостероновая система; САД – систолическое артериальное давление; ДАД – диастолическое артериальное давление; ЧСС – частота сердечных сокращений; СМАД – суточное мониторирование артериального давления; БРА – блокаторы рецепторов ангиотензина II.

INTRODUCTION

Arterial hypertension (AH) is a polygenic inherited disease and one of the major modifiable risk factors for cardiovascular events. The prevalence of AH is steadily increasing worldwide and according to the estimates by various authors, the population suffering from AH is supposed to increase by 60% over the next 20 years to more than 1.5 billion people [1].

Personalized pharmacotherapy of AH based on different variations of genes responsible for the function of drug metabolic enzymes, the genes that are involved in the pathogenetic mechanisms of the AH development and alter the pharmacodynamic effects of drugs [2–5], as well as the genes associated with drug transporters, will improve the efficacy of pharmacotherapy in AH patients who regularly receive antihypertensive drugs (AHDs) in

accordance with clinical recommendations and yet do not achieve the target blood pressure (BP) [6–8].

In the study of 2020, Patel D.D. et al. [9] studied the risk of the essential AH development in the carriers of the I/D polymorphic allele of the ACE gene polymorphism. The study included 279 AH patients and 292 healthy participants. The authors determined a statistically significant increase in the odds of developing AH at genotype D/D by I/D polymorphism of the ACE gene (OR: 2.09; 95% CI=1.24–2.91), and concluded that genetic variants of the ACE gene by I/D polymorphism may serve as a predictor of the AH development.

Angiotensin-converting enzyme (ACE) converts angiotensin I to the vasoactive angiotensin II and inactivates bradykinin. For the ACE gene, the most significant is not a single nucleotide polymorphism (SNP), but indels (insertions and deletions) of nucleotides in the genome during mutagenesis [10]. A certain DNA sequence (287 nucleotide pairs) can be inserted (insertion – I) or deleted (deletion – D) in the 16th intron of the ACE gene. The insertion/deletion polymorphism (I/D-polymorphism, a human reference sequence designation rs4340, rs4341, rs4343, rs4646994) of the ACE gene leads to a variability in serum ACE levels [11–14]. According to the meta-analysis of 2021, which included 57 studies (32 862 patients), the D allele is associated with a greater ACE activity and a higher risk of the AH development [15], which may be also the reason for the variability of the ACE efficacy in AH.

THE AIM of the work was to study pharmacodynamic parameters of the therapy efficacy with angiotensin II receptor blockers in the form of monotherapy and as part of combined drugs in patients with the arterial hypertension depending on the genetic features of patients – polymorphism of the gene encoding angiotensin-converting enzyme or I/D-polymorphism.

MATERIALS AND METHODS

The study included 179 patients of the Moscow Region with the first-time diagnosed AH I–II, among whom there were 141 (78.8%) women and 38 (21.2%) men aged from 32 to 69 years (Mean=58.2±6.4, Median is 60 (57–63 years). The study participants were searched in outpatient treatment and preventive care institutions of Moscow, clinical bases of the Department of Clinical Pharmacology and Propaedeutics of Internal Medicine I.M. Sechenov First Moscow State Medical University (Sechenov University): Moscow City Clinical Hospital named after E.O. Mukhin, Veterans Hospital No. 3 (Moscow), Central Clinical Hospital of Civil Aviation (Moscow), Moscow City Clinic No. 2.

Eligibility criteria

Patients met the following inclusion criteria: AH I–II, the age between 18 and 74 years, and a signed written informed consent from the patient to participate in the study.

The patients met the following inclusion criteria: AH III, uncontrolled AH; arterial hypotension, hypersensitivity to irbesartan and valsartan or ancillary components of the drug; an active liver disease or a more than 3-fold increase in the serum transaminase activity, a liver failure (Child-Pugh classes A and B), a chronic kidney disease stage 4–5 (glomerular filtration rate (GFR) 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 treatment with drugs affecting the renin-angiotensin-aldosterone system (RAAS), including ACE inhibitors, concomitant use of aliskiren and drugs containing aliskiren in patients with diabetes mellitus and/or moderate or severe renal dysfunction (GFR less than 60 ml/min/1.73 m^2 body surface area), concomitant use of ACE inhibitors in patients with diabetic nephropathy, galactose intolerance, lactase insufficiency and a glucose-galactose malabsorption syndrome, an established diagnosis of malignancy at the time of the inclusion in the study, need for continuous intake of non-steroidal anti-inflammatory drugs and/or drugs metabolized by cytochrome P-450 CYP2C9, which may affect the efficacy and safety profile of irbesartan.

Exclusion criteria: pregnancy, development of serious adverse drug effects, acute myocardial infarction, acute cerebral circulatory failure. No patients were excluded during the study.

Ethical approval

The study was approved by the Local Ethical Committee of I.M. Sechenov First Moscow State Medical University (Sechenov University) (Protocol No. 05-21 dated 10 March 2021). Written voluntary informed consents for participation in the study were obtained from all patients.

Study duration

The study was conducted from July 1, 2021 to August 28, 2022.

Study design

An open randomized controlled clinical trial was conducted. The program of clinical and instrumental examination of the patients included: a collection of patient's complaints, anamnesis (presence of risk factors for the AH development, concomitant diseases), a physical examination, a biochemical blood analysis, office BP measurements, electrocardiography (ECG) to exclude patients with rhythm disturbances or concomitant heart diseases, echo, daily BP monitoring (DBPM). BP was measured in both arms using the Korotkoff method after a 10-minute rest in the sitting position and was determined as the average of three measurements taken at 1-minute intervals. DBPM

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was performed when patients were enrolled in the study and after 3 months of therapy, and the values of standard daytime and nighttime DBPM parameters were assessed: a mean value, a variability of systolic BP (SBP), diastolic BP (DBP), and HR.

All patients included in the study had not previously received regular antihypertensive therapy and were randomly assigned to the irbesartan and valsartan groups by a simple randomization (an envelope method). The study participants received angiotensin II receptor blockers (ARBs) – irbesartan (Aprovel, Sanofi Winthrop Industries, France) and valsartan (Diovan, Novartis Pharma GmbH, Germany) in monotherapy or in combination with hydrochlorthiazide (Coaprovel, Sanofi Winthrop Industries, France; Co-Diovan, Novartis Pharma GmbH, Germany) for 3 months. Four groups of patients were formed: Group 1 (irbesartan 150 mg 1 per day) – 32 patients; Group 2 (irbesartan 150 mg+hydrochlorthiazide 12.5 mg 1 per day) – 51 patients; Group 3 (valsartan 80 mg 1 per day) – 8 patients; Group 4 (valsartan 80 mg+hydrochlorthiazide 12.5 mg 1 per day) – 88 patients. When the target BP values were reached after 3 weeks of therapy (<140/90 mm Hg, in case of good tolerance <130/80 mm Hg, but not <120/70 mm Hg), the patients continued to follow the prescribed therapy during 3 months of treatment. In case of an insufficient BP control, the therapy was intensified by increasing the dose of irbesartan or valsartan to 300 and 160 mg, respectively, as part of mono- or combination therapy. Three weeks after the inclusion in the study, blood was collected using a Vacuette vacuum system by venipuncture of the middle elbow or a saphenous vein to determine the genetic polymorphism rs4646994 Alu Ins/Del of the ACE gene and to determine the minimum equilibrium concentration of ARBs. Office BP measurements were 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.

Determination of genetic polymorphism

The genetic polymorphism rs4646994 Alu Ins/Del of the ACE gene was determined using the SNP-SHOT Two step kit produced by Litekh NPF LLC (Russia) and its accompanying instructions.

Study of irbesartan and valsartan concentrations

Concentrations of irbesartan and valsartan in the blood plasma were studied 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 a ME54 METTLER TOLEDO analytical scale, single-channel mechanical pipettes with variable volumes of 100–1000 µL and 20–200 µL (Thermo Scientific Black), an Eppendorf (Germany) centrifuge, and a C-18, 50×2.1 mm, 1.7 column. For the study, 250 µL of each calibration standard irbesartan solution was taken into a 1.5-mL microtube, and 250 µL of plasma was added. The final concentration of irbesartan calibration standard solutions were 2500, 1000, 500, 500, 250, 250, 100, 50, 25 and 10 ng/mL, respectively. The sample preparation was carried out in the following way: 500 µl of acetonitrile was added to 500 µl of the sample. The sample was carefully pipetted and centrifuged for 10 min at 13 200 rpm. The supernatant was withdrawn into individual microtubes and used for the analysis. For valsartan, 250 µl of each calibration standard solution was taken into a 1.5 ml microtube and 250 µl of plasma was added. The final concentration of valsartan calibration standard solutions was 2500, 1000, 500, 500, 250, 100, 50, 25, 5 and 1 ng/mL, respectively. The sample preparation was carried out in the following way: 500 µL of acetonitrile was added to 500 µL of the sample. The sample was carefully pipetted and centrifuged for 10 min at 13,200 rpm. The supernatant was collected in individual microtubes and used for analysis.

Statistical processing

The sample size was not pre-calculated.

A statistical analysis and visualization of the obtained data were performed using the R 4.2.3 statistical computing environment (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics for qualitative variables are presented as a number of observations (a relative frequency). Fisher's exact test was used to compare the groups with respect to the qualitative variables. The likelihood ratio test was used to analyze the correspondence of the empirical genotypes distribution to the theoretical one defined by the Hardy-Weinberg equilibrium. For the correlation analysis, the Spearman's rank correlation coefficient ρ with corresponding 95% confidence intervals (95% CI) was used; in the presence of a statistically significant correlation between quantitative indices, regression coefficients (with corresponding 95% CI) in single-factor regression models were estimated. To assess the strength and statistical significance of the association of quantitative predictors with binary outcomes, single-factor logistic regression models were used, herewith, their coefficients were estimated with Firth (1993) corrections for rare outcomes.

In the comparative analysis of genotype effects with changes in SBP, DPB, and HR, linear regression models with the inclusion of an interaction term between the genotype and administrated drug and robust standard errors of regression coefficients were used. 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 concentration and a single-factor genotype-dependent concentration model, which were 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 nonparametric (the standard error was estimated using a nonparametric bootstrap). The results were considered statistically significant at p <0.05.The results were considered statistically significant at p <0.05.

RESULTS

Baseline characteristics of patients

The study included 179 patients (141 (78.8%) women and 38 (21.2%) men) with AH aged 32 to 69 years (mean age was 58.2 (6.4), median age was 60 (57–63) years. O them 83 (46.4%) patients received irbesartan, 96 (53.6%) patients received valsartan, and 138 (77.1%) study participants received sartans in combination with hydrochlorthiazide, including 50 (60.2%) patients receiving ibersartan and 88 (91.7%) patients receiving valsartan (p <0.001). Table 1 shows the demographic and anamnestic characteristics of the patient groups depending on the drug prescribed. During the comparative analysis it was found that valsartan was statistically significantly more often prescribed to male patients (p <0.001), no statistically significant differences were found between the patient groups with respect to age (p=0.24). The patients receiving valsartan also had statistically significantly higher BMI and more often had obesity of the 3rd degree (p <0.001); in addition, patients in this group were statistically significantly more likely to have bronchial asthma (p=0.012) and statistically significantly less likely to have a past medical history of Crohn's disease (p=0.044).

All patients were genotyped according to the I/D polymorphism of the ACE gene, and according to the results, the groups were formed depending on the genotype. Based on the data obtained, the frequency of carriage of polymorphic allele D by I/D polymorphism of the ACE gene, which is responsible for the conversion of angiotensin I into vasoactive angiotensin II and inactivates bradykinin, amounted to 173 (48.3%), while homozygotes for mutant allele and carriers of D/D genotype were 45 patients (25.1%), and heterozygous representatives of I/D genotype – 83 (46.4%) patients. There were no statistically significant deviations of the observed frequency of genotypes for the I/D polymorphism of the ACE gene from the theoretical one determined by the Hardy-Weinberg equilibrium (G_2=0.92, p=0.338).

The minimum values of the equilibrium irbesartan concentration in patients with the I/I genotype by the I/D polymorphism of the ACE gene were determined at the level of 2346 (95% CI=1973–2616) ng/mL, with the I/D genotype – 2007 (95% CI=16582–2559) ng/mL, with the D/D genotype – 1789 (95% CI=1690–2026) ng/mL. The mean values of the minimum equilibrium valsartan concentration in patients with the I/I genotype by the I/D polymorphism of the ACE gene were determined at 1095 (95% CI=746–1580) ng/mL, with the I/D genotype – 1002 (95% CI=519–1428) ng/mL, with the D/D genotype – 1492 (95% CI=740–1685) ng/mL.

Table 2 shows the results of the assessment dynamics of SBP, DBP and HR in patients with different ACE genotypes.

No statistically significant association of the ACE genotype with a change in the office SBP among patients receiving irbesartan was found both in 3 weeks (p=0.18) and 3 months of therapy (p=0.803) (Fig. 1). Among patients receiving valsartan, after 3 weeks of therapy, I/I homozygotes had a statistically significantly greater change in the office SBP by a mean of 6.3 [95% CI=11.7; –0.8] mm Hg compared to heterozygotes (p=0.02) and by 6.5 [95% CI=12.8; –0.3] mm Hg compared to D/D homozygotes (p=0.038), with the drug concentration not being a statistically significant effect mediator (p=0.752). There was no statistically significant association of the ACE genotype with the effect of valsartan on the office SBP (p=0.225).

When assessed after 3 weeks of therapy among D/D homozygotes receiving irbesartan, there was a statistically significant less pronounced mean of 6.6 [95% CI: 0.6; 12.6] mm Hg decrease in the office BP compared with I/I homozygotes (p=0.027); the effect was not associated with the level of the equilibrium drug concentration (p=0.174) (Fig. 2). D/D homozygotes at the ACE locus taking valsartan, when assessed after 3 weeks of therapy, had a greater reduction in DBP compared to heterozygotes by 10.1 [95% CI=-17.7; -2.6] mm Hg (p=0.005) and by 6.4 [95% CI=-13.2; 0.5] compared to I/I homozygotes (p=0.075), this effect was also not associated with the valsartan equilibrium concentration level (p=0.698). There was no statistically significant association of change in DBP after 3 months of therapy with the ACE genotype (p=0.203), D/D homozygotes taking valsartan had a more pronounced reduction in DBP compared to I/I homozygotes by 10 [95% CI=-15.3; -4.7] mm Hg (p <0.001) and 5.7 [95% CI=-10.6; -0.9] mm Hg compared to heterozygotes (p=0.015), heterozygotes were also characterized by a more pronounced reduction compared to I/I homozygotes by a mean of 4.2 [95% CI=-8.8; 0.4] mm Hg (p=0.015), this effect was not associated with the equilibrium drug concentration (p=0.622).

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Table 1 – Demographic and anamnestic group dimensions of patients

Group dimensions	Irbesartan (*n*=83)	Valsartan (*n*=96)	*p*
Gender:	–	–	<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
No	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	10 (12%)	16 (17%)	0.382
Chronic tonsillitis	7 (8.4%)	4 (4.2%)	0.236
AD	2 (2.4%)	12 (13%)	0.012
Varicose veins of lower limbs	8 (9.6%)	4 (4.2%)	0.144
Migraine	2 (2.4%)	4 (4.2%)	0.687
Crohn's disease	4 (4.8%)	0 (0%)	0.044
Psoriasis	2 (2.4%)	0 (0%)	0.214
Osteochondrosis	13 (16%)	12 (13%)	0.543

Note: BMI – body mass index; AD – Alzheimer's disease.

Table 2 – SBP, DBP and HR in patients with different ACE genotypes

Characteristics	Irbesartan				Valsartan			
	I/I	I/D	D/D	*p*	I/I	I/D	D/D	*p*
Initial office SBP	156.1 (±5.6)	153.5 (±6.9)	158.7 (±8.4)	0.028*	155 (±10.5)	155.9 (±11.3)	155.2 (±10.7)	0.703
Office SBP (3 weeks)	127.8 (±10.6)	131.5 (±11.2)	136.9 (±11.7)	0.055*	136.9 (±9.7)	135.7 (±12.4)	132.3 (±13.9)	0.285
Δ office (3 weeks).	–28.3 (±10.1)	–22 (±7.8)	–21.8 (±8.6)	0.004*	–18.1 (±12.7)	–20.2 (±12.4)	–22.8 (±10.3)	0.18
p	<0.001	<0.001	<0.001	–	<0.001	<0.001	<0.001	–
Office SBP (3 months)	126.9 (±4)	126.9 (±4)	128 (±8.7)	0.105	127.6 (±5.7)	127.1 (±6.4)	125.8 (±6.2)	0.496
Δ office SBP (3 months)	–29.2 (±6.4)	–26.9 (±7.2)	–30.6 (±10.8)	0.225	–27.4 (±7.1)	–28.8 (±11.3)	–29.3 (±6.5)	0.803
p	<0.001	<0.001	<0.001	–	<0.001	<0.001	<0.001	–
Baseline office DBP	97.1 (±6.7)	96 (±7.4)	98 (±9)	0.452	91.7 (±7.2)	93.6 (±8.6)	97.5 (±7.1)	0.049*
Office DBP (3 weeks)	75.3 (±6.5)	78.1 (±8.8)	82.9 (±10)	0.008*	81.9 (±10.2)	80 (±8.2)	77.5 (±10.9)	0.192
Δ office DBP (3 weeks)	–21.8 (±7.2)	–17.9 (±8.4)	–15.2 (±9)	0.019*	–9.9 (±11.6)	–13.6 (±12.3)	–20 (±8.8)	0.011*
p	<0.001	<0.001	<0.001	–	<0.001	<0.001	<0.001	–
Office DBP (3 months)	72.1 (±2)	73.1 (±3.4)	71.9 (±4.5)	0.167	73.9 (±4.1)	71.5 (±4.4)	69.7 (±2.4)	0.001
Δ office DBP (3 months)	–25.2 (±7.6)	–23 (±7.4)	–26.2 (±9.9)	0.203	–17.9 (±5.7)	–22.1 (±9.5)	–27.8 (±7.1)	<0.001
p	<0.001	<0.001	<0.001	–	<0.001	<0.001	<0.001	–
Baseline office HR	77.5 (±3.8)	76.2 (±4.3)	78 (±3.1)	0.234	78.4 (±2.5)	77.2 (±4.9)	76.3 (±5.2)	0.164
Office HR (3 weeks)	74 (±3)	73.5 (±2)	75.4 (±2.5)	0.018*	75.3 (±8.8)	74 (±2.6)	72 (±2.6)	0.009*
Δ office HR (3 weeks)	–3.6 (±3.8)	–2.7 (±3.7)	–2.6 (±3.2)	0.707	–3.1 (±9.2)	–3.2 (±3.4)	–4.3 (±4.7)	0.103
p	<0.001	<0.001	0.001	–	0.082	<0.001	<0.001	–
Office HR (3 months)	74.4 (±2.2)	73.5 (±2.5)	74.2 (±2.6)	0.724	71.1 (±2.6)	72.7 (±2)	72.7 (±1.6)	0.016*
Δ office HR (3 months).	–3.1 (±4.1)	–2.7 (±4.6)	–3.8 (±3.3)	0.706	–7.3 (±3.4)	–4.5 (±4.3)	–3.7 (±4.7)	0.007*
p	0.002	<0.001	<0.001	–	<0.001	<0.001	<0.001	–
Achievement of target BP (3 weeks)	18/23 (78.3%)	26/39 (66.7%)	7/21 (33.3%)	0.007*	12/28 (42.9%)	16/44 (36.4%)	16/24 (66.7%)	0.053*
Dose increase (intensification of AHT)	4/23 (17.4%)	12/39 (30.8%)	13/21 (61.9%)	0.007*	20/28 (71.4%)	28/44 (63.6%)	8/24 (33.3%)	0.015*
Mean daytime SBP at baseline	153 (±8.3)	152.3 (±7.9)	151.8 (±6.3)	0.71	158.1 (±4.9)	157.6 (±6)	156.8 (±5.1)	0.384
Mean daytime SBP (3 months)	124.2 (±2.7)	125.1 (±3.3)	124.5 (±6.9)	0.132	128.3 (±2.4)	127.1 (±3.7)	126.5 (±6.3)	0.465
Δ average daytime SBP	–29.2 (±8.4)	–27.4 (±6.9)	–27.3 (±10.2)	0.455	–29.9 (±6.9)	–30.5 (±6)	–30.3 (±8.2)	0.694
p	<0.001	<0.001	<0.001	–	<0.001	<0.001	<0.001	–
Mean daytime DBP baseline	101.3 (±5.2)	100.2 (±5.4)	100.7 (±4.7)	0.733	98.9 (±3.1)	101.6 (±4.3)	98.7 (±3.8)	0.003*
Mean daytime DBP (3 months)	70.3 (±3.1)	70.1 (±3)	70.9 (±4.1)	0.519	73.1 (±3.3)	71.1 (±5)	70 (±4.5)	0.012*
Δ mean daytime DBP	–31.4 (±5.5)	–30.3 (±5.6)	–29.8 (±6.9)	0.455	–25.7 (±4.9)	–30.5 (±5.7)	–28.7 (±6.7)	0.002*
p	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	
Mean daytime HR at baseline	74.5 (±2.1)	74.5 (±3)	75.2 (±2.4)	0.756	75 (±0.9)	74.5 (±2.5)	74.5 (±2.9)	0.483
Mean daytime HR (3 months)	73.1 (±1.4)	72.7 (±1.3)	73.6 (±1.8)	0.268	71.7 (±2.5)	72.4 (±1.8)	71.8 (±0.7)	0.123
Δ mean daytime HR	–1.5 (±2.1)	–1.8 (±3.2)	–1.6 (±2.2)	0.688	–3.3 (±3.2)	–2.1 (±1.6)	–2.7 (±2.5)	0.268
p	0.004	0.001	0.003	–	<0.001	<0.001	<0.001	–
Mean nighttime SBP baseline	133.6 (±6.9)	132.3 (±5.7)	131 (±6.6)	0.37	132.7 (±6)	135.8 (±6.8)	135.2 (±2.6)	0.148

Characteristics	Irbesartan				Valsartan			
	I/I	I/D	D/D	*p*	I/I	I/D	D/D	*p*
Mean nighttime SBP (3 months)	115.2 (±3.4)	115.7 (±4.1)	116.2 (±7.2)	0.082	117.4 (±1.8)	117.1 (±3.1)	116 (±5.6)	0.872
Δ mean nighttime SBP	−18.7 (±8.5)	−16.8 (±5.9)	−14.9 (±10.9)	0.105	−15.3 (±7)	−18.7 (±8)	−19.2 (±7)	0.256
p	<0.001	<0.001	<0.001	–	<0.001	<0.001	<0.001	–
Mean nighttime MAP baseline	86.1 (±4.7)	85.5 (±5.2)	86.3 (±4.5)	0.919	86.9 (±3.7)	89.1 (±5.9)	86.8 (±3.3)	0.015*
Mean nighttime MAP (3 months)	61.1 (±4.1)	61.4 (±3.8)	58.6 (±3.3)	0.026*	62.4 (±4)	61.3 (±4.6)	60.5 (±4.5)	0.163
Δ mean nighttime MAP	−25.2 (±6)	−24.4 (±5)	−27.7 (±5.9)	0.052*	−24.4 (±4.2)	−27.8 (±6.2)	−26.3 (±6.4)	0.075
p	<0.001	<0.001	<0.001	–	<0.001	<0.001	<0.001	–
Mean nighttime HR baseline	69.3 (±2.9)	67.9 (±3.5)	68.1 (±2.5)	0.19	68 (±2.6)	67.9 (±3.5)	69 (±3.2)	0.186
Mean nighttime HR (3 months)	66.7 (±2.3)	66.1 (±2.8)	66.5 (±3.3)	0.483	63.9 (±3.5)	64.3 (±3.6)	63.7 (±2.5)	0.636
Δ mean nighttime HR	−2.6 (±3.1)	−1.9 (±4.4)	−1.6 (±3.6)	0.593	−4.1 (±4.8)	−3.6 (±3.5)	−5.3 (±5.4)	0.095
p	<0.001	0.011	0.059	–	<0.001	<0.001	<0.001	–
Daytime SBP variability baseline	17.6 (±3.6)	17.2 (±3.6)	17.5 (±3.4)	0.846	19.9 (±0.3)	19.9 (±0.3)	20 (±0.3)	0.215
Daytime SBP variability (3 months)	11.5 (±0.3)	11.5 (±0.3)	11.5 (±0.2)	0.901	11.7 (±0.2)	11.5 (±0.2)	11.6 (±0.2)	<0.001*
Δ daytime SBP variability	−6 (±3.5)	−5.8 (±3.7)	−6 (±3.3)	0.842	−8.1 (±0.3)	−8.4 (±0.5)	−8.4 (±0.5)	0.013*
p	<0.001	<0.001	<0.001	–	<0.001	<0.001	<0.001	–
Daytime DBP variability at baseline	12.5 (±1.9)	12.2 (±2)	12.1 (±1.8)	0.48	13.2 (±0.6)	13.8 (±0.5)	13.5 (±0.5)	0.002*
Daytime DBP variability (3 months)	9.7 (±0.3)	9.6 (±0.3)	9.7 (±0.3)	0.573	9.8 (±0.4)	9.7 (±0.2)	9.7 (±0.3)	0.768
Δ daytime DBP variability	−2.8 (±2)	−2.6 (±2)	−2.5 (±1.7)	0.586	−3.4 (±0.7)	−4.1 (±0.5)	−3.8 (±0.5)	<0.001*
p	<0.001	<0.001	<0.001	–	<0.001	<0.001	<0.001	–
Variability of nighttime SBP baseline	11.8 (±1.4)	11.6 (±1.4)	11.7 (±1.4)	0.842	12.5 (±0.8)	12.7 (±0.6)	12.3 (±0.9)	0.076
Nighttime SBP variability (3 months)	9.8 (±0.3)	9.8 (±0.4)	9.7 (±0.4)	0.737	9.4 (±0.3)	9.9 (±0.3)	9.8 (±0.2)	<0.001*
Δ variability of nighttime SBP	−2 (±1.4)	−1.8 (±1.4)	−1.9 (±1.4)	0.87	−3.2 (±0.8)	−2.9 (±0.8)	−2.5 (±1)	0.018*
p	<0.001	<0.001	<0.001	–	<0.001	<0.001	<0.001	–
Night DBP variability baseline	9.3 (±0.6)	9.3 (±0.7)	9.2 (±0.7)	0.77	9.8 (±0.4)	9.7 (±0.5)	9.7 (±0.7)	0.921
Night DBP variability (3 months)	8.5 (±0.3)	8.6 (±0.2)	8.5 (±0.3)	0.275	8.5 (±0.2)	8.4 (±0.2)	8.4 (±0.1)	0.077
Δ variability of nighttime DBP	−0.8 (±0.7)	−0.7 (±0.8)	−0.7 (±0.7)	0.748	−1.2 (±0.6)	−1.3 (±0.5)	−1.3 (±0.7)	0.755
p	<0.001	<0.001	<0.001	–	<0.001	<0.001	<0.001	–
Achievement of target BP (3 months)	22/22 (100%)	38/38 (100%)	20/21 (95.2%)	0.259	28/28 (100%)	40/44 (90.9%)	24/24 (100%)	0.149
ADR (arterial hypotension)	1/23 (4.3%)	1/39 (2.6%)	1/21 (4.8%)	>0.999	0/28 (0%)	4/44 (9.1%)	0/24 (0%)	0.149

Note: HR – heart rate; SBP – systolic blood pressure; DBP – diastolic blood pressure; BP – blood pressure; AHT – antihypertensive therapy; ADR – adverse drug reaction; * – statistically significant at $p < 0.05$.

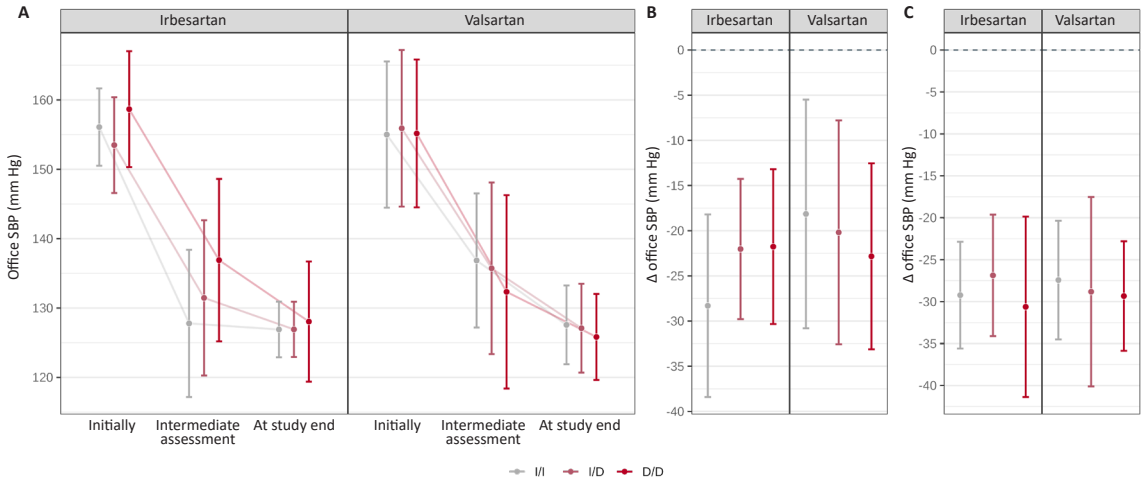

Figure 1 – Dynamics of office SBP in patients with different ACE genotypes

Note: A – dynamics of office SBP reduction during the whole study period with different ACE genotypes; B – delta of office SBP values initially and after 3 weeks with different ACE genotypes; C – delta of office SBP values after 3 weeks–3 months of therapy with different ACE genotypes; SBP – systolic blood pressure.

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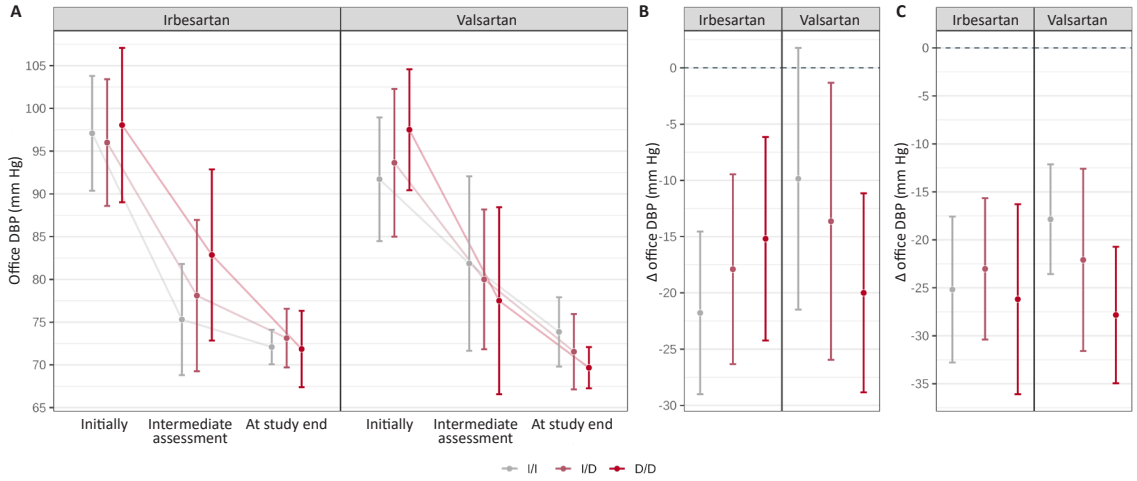

Figure 2 – Dynamics of office DBP in patients with different ACE genotypes

Note: A – dynamics of the office BP reduction during the whole study period with different ACE genotypes; B – delta of the office BP values initially and after 3 weeks with different ACE genotypes; C – delta of the office BP values after 3 weeks–3 months of therapy with different ACE genotypes; DBP – diastolic blood pressure.

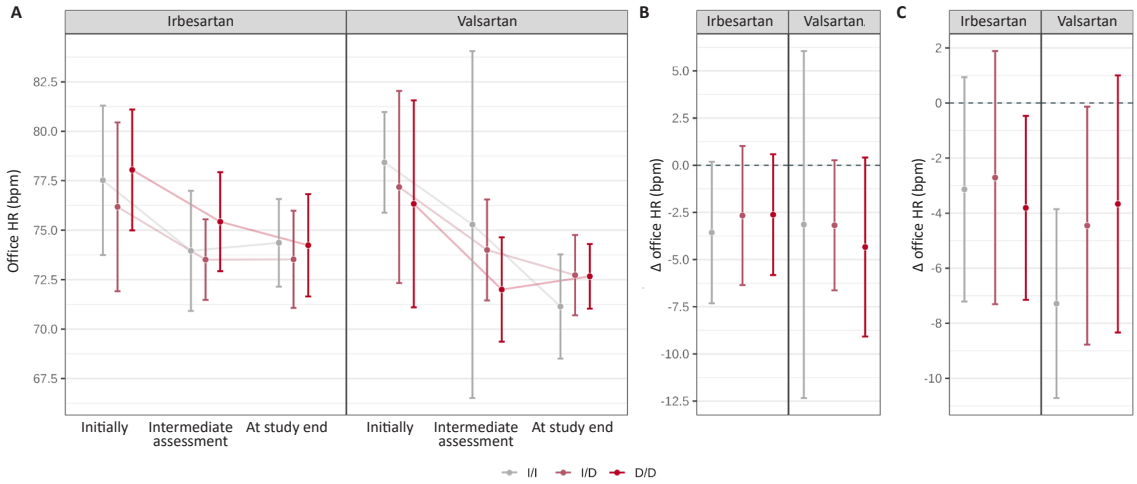

Figure 3 – Dynamics of office HR in patients with different ACE genotypes

Note: A – dynamics of the office HR reduction during the whole study period with different ACE genotypes; B – delta of the office HR values initially and after 3 weeks with different ACE genotypes; C – delta of the office HR values after 3 weeks–3 months of therapy with different ACE genotypes; HR – heart rate.

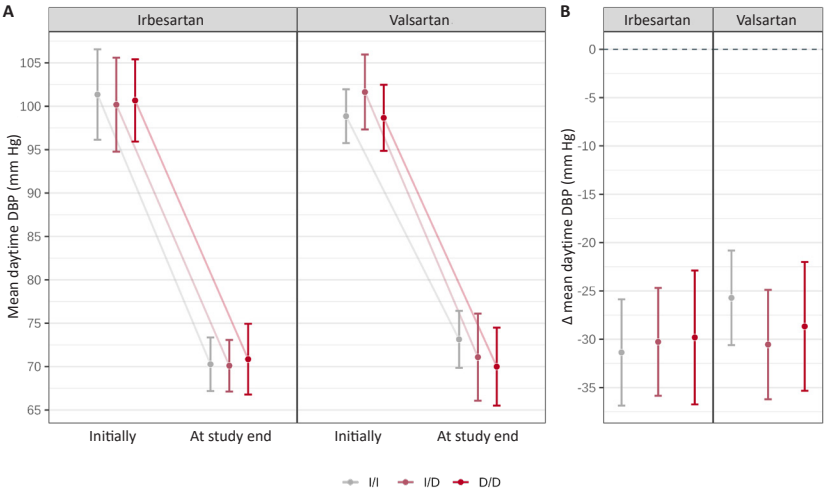

Figure 4 – Dynamics of mean daytime DBP in patients with different ACE genotypes

Note: A – dynamics of decrease in mean daytime MAP initially and after 3 months with different ACE genotypes; B – delta of mean daytime DBP values initially and after 3 months with different ACE genotypes; DBP – diastolic blood pressure.

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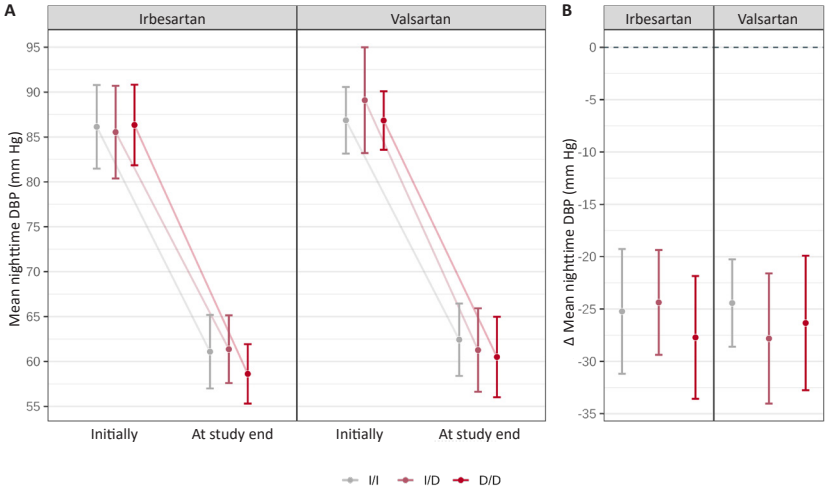

Figure 5 – Dynamics of mean night DBP in patients with different ACE genotypes

Note: A – dynamics of decrease in the mean nighttime DBP initially and after 3 months with different ACE genotypes; B – delta of the mean night DBP values initially and after 3 months with different ACE genotypes; DBP – diastolic blood pressure.

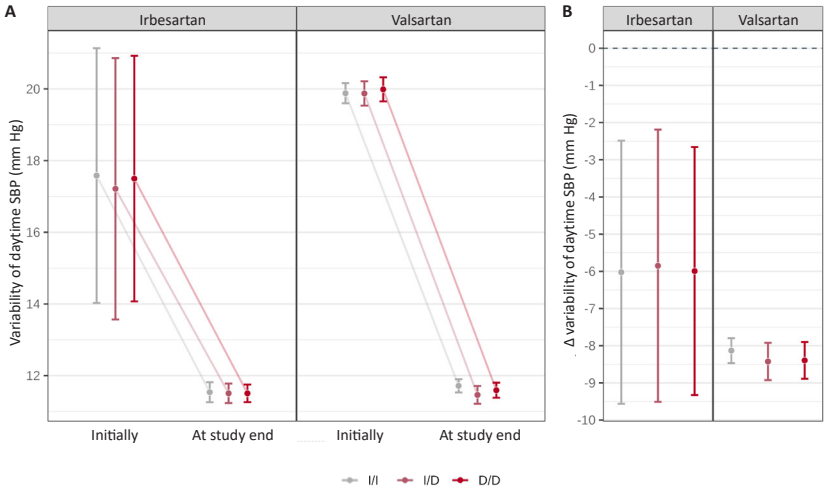

Figure 6 – Dynamics of daytime SBP variability in patients with different ACE genotypes

Note: A – dynamics of decrease in the daytime SBP variability baseline and after 3 months with different ACE genotypes; B – delta of the SBP variability values baseline–after 3 months with different ACE genotypes; SBP – systolic blood pressure.

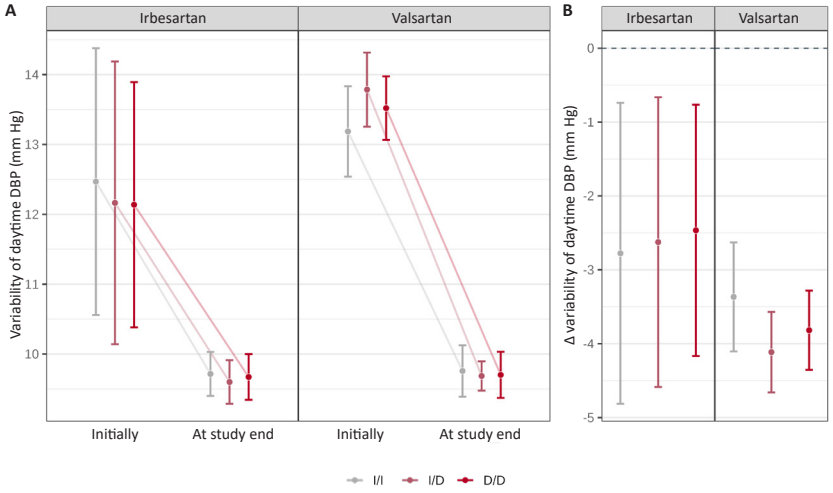

Figure 7 – Dynamics of daytime DBP variability in patients with different ACE genotypes

Note: A – dynamics of decrease in the daytime DBP variability baseline and after 3 months with different ACE genotypes; B – delta of DBP variability values baseline and after 3 months with different ACE genotypes; DBP – diastolic blood pressure.

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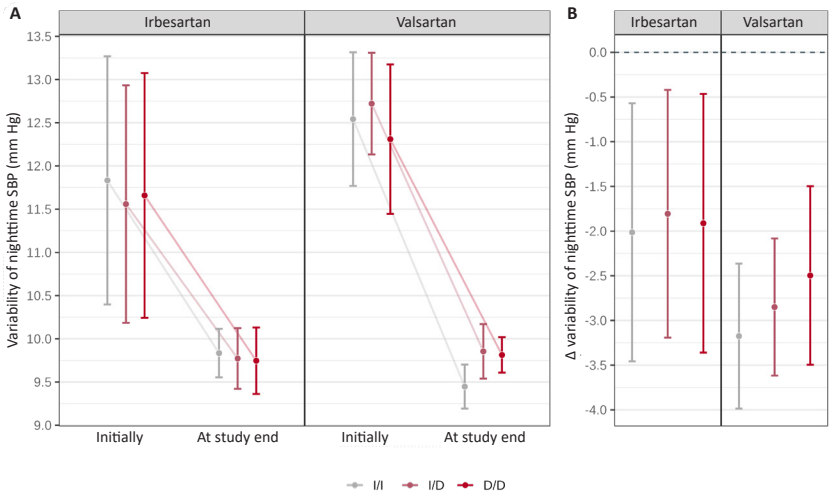

Figure 8 – Dynamics of nighttime SBP variability in patients with different ACE genotypes

Note: A – dynamics of decrease in the nighttime SBP variability baseline and after 3 months with different ACE genotypes; B – delta values of the nighttime SBP variability baseline and after 3 months with different ACE genotypes; SBP – systolic blood pressure.

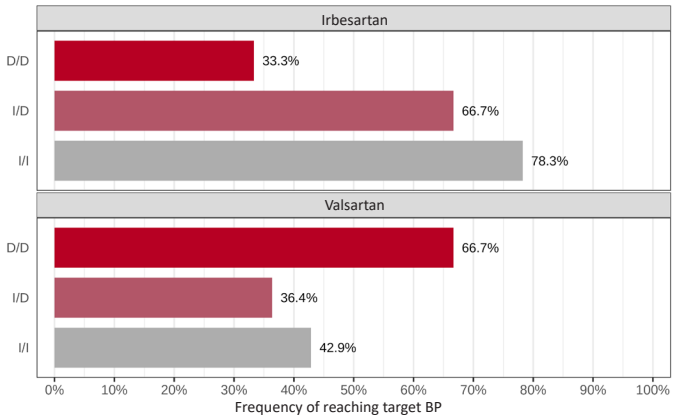

Figure 9 – Frequency of reaching target BP in patients with different ACE genotypes after 3 weeks of therapy

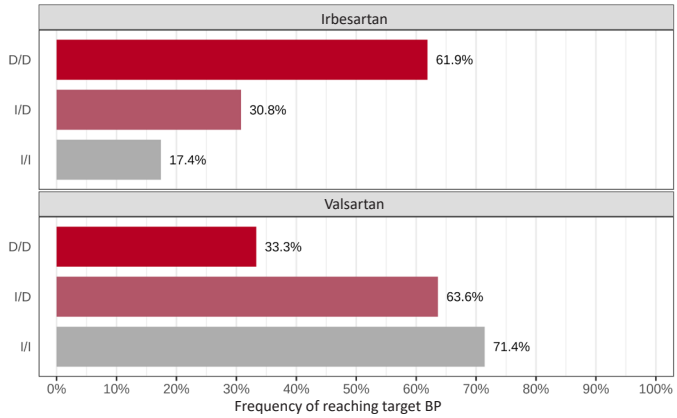

Figure 10 – Frequency of necessity to intensify antihypertensive therapy in patients with different ACE genotypes after 3 weeks of therapy

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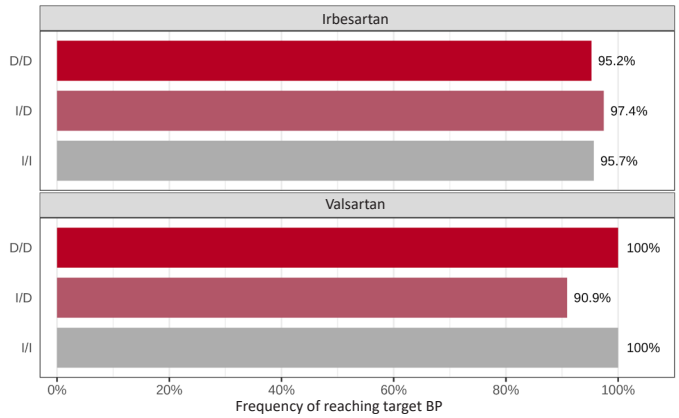

Figure 11 – Frequency of reaching target BP in patients with different ACE genotypes after 3 months of therapy

There was no statistically significant association of the ACE genotype with the change in the office HR against the background of treatment among the patients taking irbesartan both after 3 weeks and 3 months of therapy (p=0.707 and p=0.706, respectively). Among the patients taking valsartan, there was also no statistically significant association with a genotype after 3 weeks of therapy (p=0.103); however, after 3 months, the D/D homozygotes taking the drug had a less pronounced decrease in HR compared to the I/I homozygotes by 3.6 [95% CI=0.9; 6.4] bpm on average. (p=0.007), and this effect was not associated with the valsartan concentration (p=0.558) (Fig. 3).

There were no statistically significant differences with respect to the effect of irbesartan on the mean daily DBP depending on the ACE genotype (p=0.455). Heterozygotes receiving valsartan had a statistically significant greater mean 4.8 [95% CI=-8.1; -1.5] mm Hg reduction in DBP compared to I/I homozygotes (p=0.002), the effect was not associated with the equilibrium drug concentration (p=0.712) (Fig. 4).

There was a trend toward a more pronounced reduction in the mean night DBP in D/D homozygotes receiving irbesartan compared with heterozygotes by a mean of 3.3 [95% CI=-6.9; 0.2] mm Hg (p=0.071) and heterozygotes receiving valsartan compared with I/I homozygotes by a mean of 3.4 [95% CI=-6.7; 0.1] mm Hg (p=0.071) and heterozygotes receiving valsartan compared to I/I homozygotes by an average of 3.4 [95% CI=-6.7; 0.1] mm Hg (p=0.064), and these effects were not associated with the drug concentrations (p=0.726 and p=0.58, respectively) (Fig. 5).

No statistically significant association of daytime SBP variability with the genotype at the ACE locus among the patients receiving irbesartan (p=0.842) was found. Heterozygotes receiving valsartan were characterized by a more pronounced reduction in the daytime SBP variability by a mean of 0.3 [95% CI=-0.6; 0] mm Hg compared to I/I homozygotes (p=0.042). There was also a trend towards a more pronounced reduction in this parameter in D/D homozygotes by an average of 0.3 [95% CI=-0.6; 0.1] mm Hg compared to I/I homozygotes (p=0.123). These effects were not associated with the equilibrium valsartan concentration (p=0.932) (Fig. 6).

There was no statistically significant association of daytime DBP variability with the genotype at the ACE locus among patients receiving irbesartan (p=0.586). D/D homozygotes and heterozygotes receiving valsartan showed a statistically significant greater reduction in the daytime DBP variability compared to I/I homozygotes by a mean of 0.5 [95% CI: -0.9; 0] mm Hg (p=0.029) and by 0.7 [95% CI: -1.1; -0.4] mm Hg (p <0.001), respectively. This effect was not associated with the valsartan concentration (p=0.888) (Fig. 7).

There was no statistically significant association of the nighttime SBP variability with genotype at the ACE locus among patients receiving irbesartan (p=0.87). D/D homozygotes receiving valsartan compared with I/I homozygotes had a less pronounced drug effect on the nighttime SBP variability (p=0.019) by 0.7 [95% CI=0.1; 1.3] mm Hg, with the equilibrium concentration of irbesartan not being a statistically significant mediator (p=0.89) (Fig. 8).

Among the patients taking irbesartan, the D/D genotype was characterized by the lowest frequency of reaching the target BP after 3 weeks of therapy (p=0.011 and p=0.042 compared to homozygotes I/I and heterozygotes, respectively) (Fig. 9) and the highest frequency of the drug dose increase necessity (p=0.011 and p=0.058 compared to homozygotes I/I and heterozygotes, respectively) (Fig. 10).

Among the patients taking valsartan, the D/D genotype was characterized by a higher frequency of reaching the target BP when assessed after 3 weeks of therapy compared to heterozygotes (p=0.05), and the lowest need for the drug dose increase (p=0.021 and p=0.05 compared to I/I homozygotes and heterozygotes, respectively). The target BP achievement after 3 months of therapy was not statistically significantly associated with the ACE genotype with irbesartan (p=0.259) and valsartan (p=0.149) (Fig. 11).

There was no statistically significant association

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of the incidence of arterial hypotension with the ACE genotype among the patients treated with irbesartan (p >0.999) or valsartan (p=0.149).

DISCUSSION

Racial differences in the ACE gene polymorphism are well known. For example, in the United States, African Americans have the highest frequency of the D allele (89%) compared with Native Americans (69%) and Caucasians (69%) [16]. In Europe, the populations of Italy, Spain and France, also have a high frequency of the D allele (82–87%) [17]. In contrast, in Asia, Chinese, Koreans, Taiwanese, and Japanese, have a high frequency of the I allele of the ACE gene, which is higher than in European populations (33–51% in Asian countries *vs* 13–27% in European countries) [18]. According to the results of the present study, the frequency of the D allele carriage of the I/D polymorphism of the ACE gene is 48.3% among patients with the first-time diagnosed AH I–II in the Moscow Region.

Heidari F. et al. [19] studied the effect of the I/D polymorphism of the ACE gene on the efficacy of therapy with enalapril and lisinopril. Thus, the reduction of SBP and DBP in the D/D genotype carriers amounted to 18.5±8.1 and 15.29±7.1 mm Hg, in the I/D genotype carriers – 4.1±3.3 and 9.1±3.5 mm Hg and the I/I genotype carriers – 3.0±0.2 and 0.11±6.1 mm Hg.

In the study by Yu H. et al. [20], 517 patients were examined. In them, the D/D genotype was determined in 132 patients (25.5%), I/D – in 255 (49.3%), I/I – in 130 (25.2%). But against the background of imidapril or benazepril therapy, no significant effect of the I/D polymorphism of the ACE gene on the BP reduction degree was revealed.

In the study SILVHIA (Swedish Irbesertan Left Ventricular Hypertrophy Investigation *vs* Atenolol, Swedish Irbesartan *vs* Atenolol on Left Ventricular Hypertrophy which included 86 patients), Kurland L. et al. [21], on the contrary, showed a significantly more pronounced decrease in BP in the genotype I/I carriers, when using ARBs irbesartan compared to the of D allele carriers.

A possible influence of the I/D polymorphism of the ACE gene on the effectiveness of ACE and long-term outcomes in patients with AH was studied by Arnett D.K. et al. [22] as part of the well-known ALLHAT (Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial) study. An additional part of the study on the influence of genetics on the efficacy of AHDs (GenHAT – The Genetics of Hypertension-Associated Treatment) involved 37,939 patients with AH aged 55 years and older, randomized to chlorthalidone, amlodipine, lisinopril, and doxazosin groups. The D/D genotype was statistically significantly (p <0.0001) more frequent than the I/D and I/I genotypes in negroids compared to Caucasoid individuals. After 6 months from the therapy start, reliable results (a more pronounced BP reduction in patients with the D/D genotype compared with the I/D and I/I ones) were obtained only in the doxazosin group. Patients with the I/D and I/I genotypes responded to the lisinopril therapy better, but these data were not statistically significant. The total duration of the patient follow-up ranged from 4 to 8 years. The following endpoints were evaluated: fatal/non-fatal myocardial infarction, development of CHD, ACVA. The study demonstrated the absence of statistically significant effect of the ACE gene I/D polymorphism on the risk of the CVS development on the background of the AHDs.

Parving H.H. et al. [23] studied the effect of the I/D polymorphism of the ACE gene on the the efficacy of therapy with losartan and placebo in 1435 patients with type 2 DM. The risk of the serum creatinine concentration increase twice as high as baseline, the risk of the terminal renal failure and mortality was evaluated. In the placebo group, the risk of reaching the combined endpoint was significantly higher among patients with the I/D and D/D genotypes, compared to I/I (by 17.5 and 38.1%, respectively, p=0.029). Compared to placebo, there was a significant effect of a genotype on the risk of reaching the combined endpoint among the patients receiving losartan, by 5.8% (95% CI=23.3-28.0), 17.6% (95% CI=3.8-29.4) and 27.9% (95% CI=7.0-44.1) among the patients with the I/I, I/D and D/D genotypes, respectively.

Rohman M.S. et al. [24] studied the influence of the I/D polymorphism of the ACE gene and the T/C polymorphism of the bradykinin B_2 receptor gene on the dry cough development risk against the background of ACE inhibitors. The study included 18 patients with cough and 67 patients taking ACE inhibitors without cough. In addition, the authors performed a meta-analysis of 5 clinical trials (267 patients with cough/346 without cough). From both the study of their own and the meta-analysis, the authors found no significant effect of the ACE gene I/D polymorphism on the risk of cough when using ACE inhibitors. However, according to the results of the meta-analysis, the T-allele of the bradykinin B_2 receptor gene was associated with a 1.82-fold increase in the risk of the dry cough development during the use of ACE inhibitors (p=0.031).

In the Russian Federation, I/D polymorphism of the ACE gene is poorly studied. A small domestic study, which included 35 patients (24% – D/D genotype, 55% – I/D and 10% – I/I), showed a greater efficacy of the telmisartan therapy, which was evaluated by the effect on the myocardial mass index of the left ventricle, in the group of heterozygotes (the I/D genotype) [25]. Rebrova T.Y. et al. [26] studied the I/D polymorphism of the ACE gene in 173 patients diagnosed with a coronary heart disease who had undergone a heart attack (HA) and in 153 healthy people of the same age (24.5% – I/I genotype, 53.1% – I/D and 22.4% – D/D). The men who had undergone HA had a statistically significantly

higher frequency of the D/D genotype compared to the healthy individuals (p=0.038).

Thus, a limited number of the studies on the effect of the ACE gene I/D polymorphism on the ACE efficacy have been performed, and the data from these studies are contradictory.

The findings obtained by the authors, indicate that when assessed for the efficacy 3 weeks after the prescribed antihypertensive therapy, the genotype I/I carriers treated with valsartan, had significantly greater reductions in the office CAD by 6.3 mm Hg [95% CI=-11.7; -0.8] compared with I/D heterozygotes (p=0.02), and by 6.5 mm Hg [95% CI=12.8; -0.3] compared with D/D homozygotes (p=0.038). Herewith, the valsartan concentration was not a statistically significant effect mediator (p=0.752). At the same time, the office DBP level was more intensively decreased by 10.1 mm Hg in the D/D genotype carriers [95% CI=-17.7; -2.6] compared to the I/D genotype (p=0.005) and by 6.4 mm Hg [95% CI=-13.2; 0.5] compared with I/I homozygotes (p=0.075), and the effects were not associated with the valsartan concentration (p=0.698). After 3 months of therapy, the office DBP level of patients in the valsartan group, the carriers of the D/D genotype, showed a significantly more intensive reduction of 10 mm Hg [95% CI=-15.3; -4.7] compared to the I/I genotype (p <0.001) and by 5.7 mm Hg [95% CI=-10.6; -0.9] compared with I/D heterozygotes (p=0.015), and I/D heterozygotes – by 4.2 mm Hg [95% CI=-8.8; 0.4] compared with the I/I genotype (p=0.015). This effect was not associated with the valsartan concentration (p=0.622). According to the data obtained, the office HR in the valsartan group at the end of the study was significantly less reduced by 3.6 bpm [95% CI=0.9; 6.4] in the D/D genotype carriers compared to the I/I genotype carriers (p=0.007). According to the DBPM data, after 3 months of therapy, the patients taking valsartan, I/D heterozygotes, were significantly more likely to reduce the mean daytime DBP by 4.8 mm Hg [95% CI=-8.1; -1.5], and there was a trend toward a significantly greater reduction in the mean nighttime DBP by 3.4 mm Hg [95% CI=-6.7; 0.1] compared with I/I homozygotes (p=0.002 and p=0.064, respectively). Herewith, the effects were not associated with the level of the valsartan concentration (p=0.712 and p=0.58, respectively). There was also a significant effect of valsartan on the BP variability parameters when comparing the results of the baseline and after 3 months of the DBPM therapy. Thus, in the I/D genotype carriers, the daytime SBP variability decreased significantly more by 0.3 mm Hg [95% CI=-0.6; 0] compared to the I/I genotype carriers (p=0.042), and there was a tendency for the D/D genotype carriers to decrease the daytime SBP variability more by 0.3 mm Hg [95% CI=-0.6; 0] compared with I/I homozygotes (p=0.123). Meanwhile, the valsartan concentration was not a statistically significant mediator of the effect (p=0.932). The D/D genotype carrying who received valsartan, reduced the daytime DBP variability compared to I/I homozygotes (p=0.029 significantly more than 0.5 mm Hg [95% CI=-0.9; 0]). Herewith, heterozygotes for the I/D polymorphism of the ACE gene, reduced the daytime DBP variability by 0.7 mm Hg [95% CI=-1.1: -0.4] compared with I/I (p <0.001). The effects were not associated with the valsartan concentration (p=0.888). The nighttime SBP variability was significantly more reduced by 0.7 mm Hg [95% CI: 0.1; 1.3] in the genotype D/D patients *vs* the genotype I/I carriers (p=0.019). The effect was not associated with the drug concentration (p=0.89). Thus, the obtained statistically significant reduction of the daytime SBP variability, the daytime DBP and the nighttime SBP in the D allele carriers may indicate a more persistent effect of the antihypertensive therapy.

In the efficacy assessment of the irbesartan pharmacotherapy 3 weeks later, it was evidenced that the D/D genotype carriers by the I/D polymorphism of the ACE gene significantly reduced the level of the office DBP by 6.6 mm Hg [95% CI=0.6; 12.6] compared to the representatives of the I/I genotype (p=0.027). The effect was not associated with the irbesartan concentration (p=0.174). The authors also determined the tendency of the genotype I/D polymorphism influence of the ACE gene on the mean DBP level according to DBPM in irbesartan patients. The D/D genotype was associated with a greater reduction of this parameter by 3.3 mm Hg [95% CI=-6.9; 0.2] compared with the I/D genotype (p=0.071). The effect was not associated with the drug concentration (p=0.726).

Study limitations

This study focuses on the effect on the risk of AH and the efficacy of AHDs of a single polymorphism of a candidate gene that converts angiotensin I to vasoactive angiotensin II and inactivates bradykinin. However, the risk of the AH development and/or efficacy of AHT may be also influenced by polymorphisms in the genes involved in the AGP metabolism, responsible for a certain link of the RAAS, involved in the pathogenetic mechanisms of the AH development and influencing the pharmacodynamic effects of drugs, modifications of mechanical interactions between the drugs and genes, as well as polymorphisms in the genes associated with drug transporters, which requires a further study. The study is limited by the sample size and region.

CONCLUSION

The analysis of the BP target achievement and the need for the intensification of pharmacotherapy after 3 weeks of therapy showed significant results depending on the main drug. Thus, the D/D genotype irbesartan carriers were significantly less likely to reach the target

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BP and more likely to require the pharmacotherapy intensification compared with I/D heterozygotes (p=0.042 and p=0.058, respectively) and I/I homozygotes (p=0.011 and p=0.011, respectively). While the D/D genotype valsartan carriers were significantly more likely to reach the target BP, they were significantly less likely to require the pharmacotherapy intensification than the I/D genotype carriers (p=0.05 and p=0.05, respectively). At the same time, according to the results of the office BP measurements and DBPM at the end of the study, the achievement of the target BP was not significantly correlated with the I/D polymorphism of the ACE gene. Based on the obtained data, for a more effective achievement of the target BP, when personalizing the AH therapy in the Moscow Region patients, the genotype I/I carriers by the I/D polymorphism of the ACE gene, can be recommended irbesartan as a starting therapy of ARBs in the form of mono- or bicomponent therapy depending on the degree of AH, while the genotype D/D carriers can be recommended valsartan.

A more pronounced decrease in the daytime SBP variability, the daytime DBP and the nighttime DBP in the valsartan patients carrying the D allele, can indicate a more persistent effect of the antihypertensive therapy.

This study focuses on a single polymorphism responsible for a particular RAAS link and influencing the risk of the AH development and the efficacy of the ARBs therapy, while the response to antihypertensive therapy also depends on the genes involved the 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 the drug transporters. These factors determine the need for a further study of the polymorphisms influence of the candidate genes panel.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

All the authors have made equivalent and equal contributions to the publication. All the authors confirm that their authorship meets the ICMJE international criteria (all the authors made a substantial contribution to the conceptualization, research and preparation of the article, read and approved the final version before the publication). Ekaterina V. Rebrova – collection and processing of materials, conducting the study, writing the manuscript; Evgenia V. Shikh – conducting the study, editing the manuscript.

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