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Evaluation of the relationship between the minimum steady-state concentration of angiotensin II receptor blockers and polymorphic markers of *CYP2C9 (Arg144Cys)*, *CYP2C9 (IIE359Leu)*, *AGTR1 (A1166C)*, *AGT (Met235Thr, C4072T)*, *ACE (I/D)*, *CYP11B2 (C-344T)* genes and office arterial pressure

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The aim of the work was to study the relationship of the minimum steady-state concentration of angiotensin II receptor blockers with polymorphic markers of *CYP2C9 (Arg144Cys)*, *CYP2C9 (Ile359Leu)*, *AGTR1 (A1166C)*, *AGT (Met235Thr, C4072T)*, *ACE (I/D)*, *CYP11B2 (C-344T)* genes and the office blood pressure (BP) indices.

Materials and methods. The study included 179 patients of the Moscow region with newly diagnosed hypertension of stages 1–2, among whom there were 141 (78.8%) women and 38 (21.2%) men aged from 32 to 69 years (mean age — 58.2±6.4, median age — 60 (57–63 years), who had been randomized into treatment groups with valsartan and irbesartan in the form of mono- or combination therapy with hydrochlorothiazide. After 3 weeks of pharmacotherapy, polymorphic markers CYP2C9 *(Arg144Cys)*, *CYP2C9 (Ile359Leu)*, *AGTR1 (A1166C)*, *AGT (Met235Thr*, *C4072T)*, *ACE (I/D)*, *CYP11B2 (C-344T)* were genotyped and the minimum steady-state concentrations of irbesartan and valsartan were determined. The office BP measurements were performed on each visit.

Results. The carriers of alleles *2 and *3 of the *CYP2C9* gene, the genotype T/T of the *AGT* gene, the genotype I/I of the *ACE I/D* polymorphism achieved higher values of the minimum steady-state concentration of irbesartan after 3 weeks of pharmacotherapy. Homozygotes A/A for the genetic polymorphism of the *AGTR1* gene *(A1166C)*, homozygotes D/D for the *ACE I/D* polymorphism reached significantly higher values of the minimum-steady concentration of valsartan after 3 weeks of pharmacotherapy. In the patients taking irbesartan, a more pronounced decrease in the office systolic (SBP) and diastolic (DBP) BP was detected with an increase in the concentration for every 100 ng/mL after 3 weeks of therapy. Any association of the indicators with the valsartan concentration was found out.

Conclusion. The effects of irbesartan and valsartan indicate a maximum modulation of pharmacodynamic effects during 3 weeks of pharmacotherapy, followed by a consolidation in the therapeutic range and a stop in the increasing the effectiveness with a further increase in the steady-state concentration, which can be used to predict therapy, personalize it, a better control and a high safety profile.

Keywords: arterial hypertension; *CYP2C9; AGTR1; AGT; ACE; CYP11B;* irbesartan; valsartan; plasma concentration

Abbreviations: AH — arterial hypertension; BP — blood pressure; RAAS — renin-angiotensin-aldosterone system; *CYP2C9* — cytochrome P450, family 2, subfamily C, polypeptide 9; *AGTR1* — angiotensin II type 1 receptor gene, *AGT* — angiotensinogen gene; *ACE* gene — angiotensin-converting enzyme gene; *CYP11B2* — aldosterone synthase gene; GFR — glomerular filtration rate; ACE — angiotensin-converting enzyme; ARB — angiotensin II receptor blockers; CI — confidence interval; OR — odds ratio; SBP — systolic blood pressure; DBP — diastolic blood pressure; HR — heart rate.

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Оценка взаимосвязи минимальной равновесной концентрации блокаторов рецепторов ангиотензина II с полиморфными маркерами генов *CYP2C9 (Arg144Cys), CYP2C9 (Ile359Leu), AGTR1 (A1166C), AGT (Met235Thr, C4072T), ACE (I/D), CYP11B2 (C-344T)* и показателями офисного артериального давления

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Цель. Изучить взаимосвязь минимальной равновесной концентрации блокаторов рецепторов ангиотензина II с полиморфными маркерами генов *CYP2C9 (Arg144Cys), CYP2C9 (Ile359Leu), AGTR1 (A1166C), AGT (Met235Thr, C4072T), ACE (I/D), CYP11B2 (C-344T)* и показателей офисного артериального давления (АД).

Материалы и методы. В исследование включено 179 пациентов Московского региона с впервые выявленной артериальной гипертензией (АГ) 1–2 степени, среди которых 141 (78,8%) женщина и 38 (21,2%) мужчин в возрасте от 32 до 69 лет (средний возраст — 58,2±6,4, медианный возраст — 60 (57–63 лет), которые были рандомизированы по группам лечения валсартаном и ирбесартаном в виде моно- или комбинированной терапии с гидрохлортиазидом. Через 3 нед. фармакотерапии проводили генотипирование по полиморфным маркерам *CYP2C9 (Arg144Cys), CYP2C9 (Ile359Leu), AGTR1 (A1166C), AGT (Met235Thr, C4072T), ACE (I/D), CYP11B2 (C-344T)* и определение минимальной равновесной концентрации ирбесартана и валсартана. Офисное измерение АД выполняли на каждом визите.

Результаты. Носители аллелей *2 и *3 гена *CYP2C9*, генотипа T/T гена *AGT*, генотипа I/I по I/D-полиморфизму *ACE* достигали более высоких значений минимальной равновесной концентрации ирбесартана через 3 нед. фармакотерапии. Гомозиготы A/A по генетическому полиморфизму гена *AGTR1 (A1166C)*, гомозиготы D/D по I/D полиморфизму *ACE* достигали более высоких значений минимальной равновесной концентрации валсартана через 3 нед. фармакотерапии. У пациентов, принимавших ирбесартан, было выявлено более выраженное снижение офисного систолического (САД) и диастолического (ДАД) АД при увеличении концентрации на каждые 100 нг/мл через 3 нед. терапии. Ассоциации показателей с концентрацией валсартана установлено не было.

Заключение. Эффекты ирбесартана и валсартана свидетельствуют о максимальной модуляции фармакодинамических эффектов в течение 3 нед. фармакотерапии с последующим закреплением в терапевтическом диапазоне и остановкой в увеличении эффективности при дальнейшем увеличении равновесной концентрации, что может быть использовано для прогнозирования терапии, её персонализации, лучшего контроля и высокого профиля безопасности.

Ключевые слова: артериальная гипертензия*; CYP2C9; AGTR1; AGT; ACE; CYP11B;* ирбесартан; валсартан; равновесная концентрация

Список сокращений: АГ — артериальная гиперетензия; АД — артериальное давление; РААС — ренеин-ангиотензин-альдостероновая система; *CYP2C9* — цитохром P450, семейство 2, субсемейство C, полипептид 9; *AGTR1* — ген рецептора 1-го типа ангиотензина II, *AGT* — ген ангиотензиногена; *ACE* — ген ангиотензинпревращающего фермента; *CYP11B2* — ген альдостерон синтазы; СКФ — скорость клубочковой фильтрации; АПФ — ангиотензинпревращающий фермент; БРА — блокаторы рецепторов ангиотензина II; ДИ — доверительный интервал; ОШ — отношение шансов; САД — систолическое артериальное давление; ДАД — диастолическое артериальное давление; ЧСС — частота сердечных сокращений.

INTRODUCTION

Arterial hypertension (AH) is one of the most significant global health problems [1, 2], affecting 16 to 37% of the adult population worldwide [3–5]. A high prevalence of this disease causes its significant impact on the mortality and morbidity, as it is a leading risk factor for cardiovascular accidents [6], including a coronary heart disease [7], acute cerebrovascular disorders [8], a heart failure and a peripheral vascular disease [9, 10].

A blood pressure (BP) regulation is a complex multifactorial process involving the renin-angiotensin-aldosterone system (RAAS) [11, 12], natriuretic peptides [13], endothelial mechanisms [14], a sympathetic nervous system and immune processes [15,

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16]. The current studies show that a genetic predisposition to it covers a wide range of genetic variations, from rare monogenic mutations to polygenic associations involving more than 1500 single-nucleotide polymorphisms [18, 19].

The development of pharmacogenomics has significantly expanded the understanding of the complex causal relationships between the BP levels, genetic and epigenetic factors, and the risk of hypertensive complications. The first advances in this field have opened new perspectives for a personalized approach to the antihypertensive therapy aimed at optimizing the treatment efficacy and reducing the risk of side effects. The introduction of the personalized medicine principles in the management of hypertension patients can contribute not only to a more accurate selection of antihypertensive drugs, but also to the improvement of a long-term prognosis through an individualized control of risk factors.

THE AIM of the work was to study the relationship of the minimum steady-state concentration of angiotensin II receptor blockers with polymorphic markers of *CYP2C9 (Arg144Cys)*, *CYP2C9 (Ile359Leu)*, *AGTR1 (A1166C)*, *AGT (Met235Thr*, *C4072T)*, *ACE (I/D)*, *CYP11B2 (C-344T)* genes and the office blood pressure indices.

MATERIALS AND METHODS

The study design was an open randomized controlled pharmacogenetic and pharmacokinetic clinical trial.

The study included 179 patients of the Moscow region with newly diagnosed hypertension of stages 1–2, among whom there were141 (78.8%) women and 38 (21.2%) men aged from 32 to 69 years (mean age — 58.2±6.4, median age — 60 (57–63 years).

Eligibility criteria

The patients met the following *inclusion criteria*: hypertension of stages 1–2; the age between 18 and 74 years; a signed written informed consent from the patient to participate in the study.

The *non-inclusion criteria* of the patients in the study were as follows: hypertension of stage 3; the uncontrolled arterial hypotension; hypersensitivity to irbesartan and valsartan or excipients of the drugs; an active liver disease or an increase in the serum transaminase activity more than 3-fold, the liver failure (Child-Pugh classes A and B); a chronic kidney disease of stages 4–5 (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 oedema; during treatment with the drugs affecting the RAAS, including angiotensin-converting enzyme (ACE) inhibitors, a concomitant use of aliskiren and the drugs containing aliskiren in the 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 with ACE inhibitors in the patients with diabetic nephropathy; galactose intolerance, lactase insufficiency and a glucose-galactose malabsorption syndrome; an established diagnosis of malignancy at the inclusion time in the study; the need for a continuous intake of non-steroidal anti-inflammatory drugs and/or the drugs metabolized by cytochrome P-450 *CYP2C9*, which can affect the efficacy and safety profile of irbesartan.

Exclusion criteria: pregnancy, a development of serious adverse drug reactions, an acute myocardial infarction, an acute cerebral circulatory failure. No patient dropped out of the study.

Study duration

The patients were recruited from 1 July 2021 to 28 August 2022. The selection of the 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, Municipal Polyclinic No. 2.

Randomization procedure

All the patients included in the study had not previously received regular antihypertensive therapy and were randomly allocated to the irbesartan and valsartan groups by a simple randomization (an envelope method).

Study methodology

The study participants received ARBs irbesartan (Aprovel, Sanofi Winthrop Industries, France) and valsartan (Diovan, Novartis Pharma GmbH, Germany) in monotherapy or in the 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 once daily) — 32 patients; Group 2 (irbesartan 150 mg+hydrochlorothiazide 12.5 mg once daily) — 51 patients; Group 3 (valsartan 80 mg once daily) — 8 patients; Group 4 (valsartan 80 mg+hydrochlorothiazide 12.5 mg once daily) — 88 patients. When the target

BP values were achieved after 3 weeks of therapy (<140/90 mmHg, if well tolerated <130/80 mmHg, but not <120/70 mmHg), the patients continued to follow the prescribed therapy during 3 months of treatment. In case of the insufficient BP control, the intensification of therapy was performed by increasing the dose of irbesartan or valsartan to 300 and 160 mg, respectively, as a part of mono- or combination therapy.

Three weeks after the inclusion in the study, the blood was drawn by a Vacuette vacuum system (Shandong Chengwu Medical Products Factory, China) by a venipuncture of the middle elbow or saphenous vein to determine the genetic polymorphisms of *CYP2C9*2* (*Arg144Cys*) and *CYP2C9*3* (*Ile359Leu*), rs5186 (*A1166C*) of angiotensin II type 1 receptor gene *AGTR1*, rs699 (*Met235Thr*) of the angiotensinogen gene *AGT*, rs4646994 of Alu Ins/Del of the angiotensin-converting enzyme gene *ACE*, rs1799998 (*C-344T*) of the aldosterone synthase gene *CYP11B2*. The determination of the minimum-steady concentration of ARBs was carried out. The office BP measurements were performed at each visit: at the study inclusion, at intermediate stages after 3 weeks and after 3 months of therapy. BP was measured on both arms using the Korotkoff method after a 10-minute rest of the patient in the sitting position, and was determined as the average of three measurements taken at 1-minute intervals [20–22].

Determination of genetic polymorphism

To determine genetic polymorphisms, a real-time PCR method on the DNA amplifier "CFX96 Touch Real Time System" with software "CFX Manager" from BioRad (USA) and commercial kits were used.

The detection of the *CYP2C9*2* (*Arg144Cys*) and *CYP2C9*3* (*Ile359Leu*) alleles was performed using the RealBest-Genetika Warfarin kit manufactured by VectorBest (Russia), based on PCR followed by analysis of the melting curves of the resulting amplicons.

The genetic polymorphism rs5186 (*A1166C*) of the angiotensin II type 1 receptor gene *AGTR1* was determined using a reagent kit for a real-time polymorphism detection in the human genome "SNP-EXPRESS" manufactured by Litech Research and Development Company LLC (Russia).

The genetic polymorphism rs699 (*Met235Thr*) of the angiotensinogen *AGT* gene was determined using a reagent kit for a real-time polymorphism detection in the human genome "SNP-EXPRESS" produced by Litech Research and Development Company LLC (Russia).

The genetic polymorphism rs4646994 Alu Ins/Del of the angiotensin-converting enzyme *ACE* gene was determined using the "SNP-SHOT" Two-step kit produced by Litech Research and Development Company LLC (Russia) and its accompanying instructions.

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" ZAO NPK Syntol (Russia).

Irbesartan and valsartan concentration study

Irbesartan and valsartan concentrations in blood plasma were studied using HPLC on an Agilent 1290 Infinity II LC liquid chromatograph coupled with the 6470 Triple Quadrupole LC/MS (Agilent Technologies, USA) using standard calibration solutions with concentrations of 2500, 1000, 500, 250, 100, 50, 25 and 10 ng/mL, trifluoroacetic acid acid, acetonitrile and purified Milli-Q water for HPLC. The additional equipment included ME54 METTLER TOLEDO analytical scales (USA), single-channel mechanical pipettes with variable volumes of 100–1000 and 20–200 µl (Thermo Scientific Black), a centrifuge (Eppendorf, Germany), C-18 column, 50×2.1 mm, 1.7 µm, a liquid chromatograph. 250 µl of each calibration standard solution of irbesartan was transferred into a 1.5 mL microtube, 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 such a way — 500 µl of acetonitrile was added to 500 µl of the sample. It was carefully pipetted and centrifuged for 10 min at 13 200 rpm. The supernatant was collected in individual microtubes and used for the analysis.

250 µl of each valsartan calibration standard solution was transferred to a 1.5 mL microtube and 250 µl of the plasma obtained by centrifugation was added. The final concentrations of the valsartan calibration standard solutions were 2500, 1000, 500, 500, 250, 100, 50, 25, 5 and 1 ng/mL, respectively. The sample preparation was carried out in such a 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 the analysis.

Ethical approval

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

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Statistical analysis

The sample size had not been pre-calculated. The statistical analysis and visualisation of the obtained data were performed using an R 4.2.3 statistical computing environment (The R Foundation, Austria). The descriptive statistics for quantitative variables without a pronounced asymmetry of conditional sampling distributions are presented as a mean (±standard deviation, M+SD), for quantitative variables with a pronounced asymmetry (absolute values of the asymmetry coefficient >1.96) — as a median (1^{st} and 3^{rd} sample quartiles), Me (Q1–Q3). Descriptive statistics for the qualitative variables are presented as a number of observations (relative frequency, %). The 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 distribution of genotypes 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% CIs) was used, and regression coefficients (with corresponding 95% CIs) in single-factor regression models were estimated if there was a statistically significant correlation between quantitative indices. To assess the strength and statistical significance of the association of quantitative predictors with binary outcomes, single-factor logistic regression models were used, with coefficients estimated with the Firth (1993) adjustment for rare outcomes.

Linear regression models with the inclusion of an interaction term between the genotype and drug used and robust standard errors of the regression coefficients were used to compare the effects of the genotypes with changes in systolic (SBP), diastolic (DBP) BP and heart rate (HR). To assess a 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. They 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 (a standard error was estimated using a nonparametric estimator). The association was considered statistically significant at p <0.05 [20–22].

RESULTS

Table 1 and Figure 1 show comparative analysis results of the minimum steady-state drugs concentrations depending on the use of hydrochlorthiazide. Higher concentrations of irbesartan (p <0.001) and valsartan (p=0.011) were achieved with monotherapy.

In the comparative analysis, a difference regarding the effect of the *CYP2C9* (*Arg144Cys*) genotype in the use of irbesartan and valsartan was found out (p=0.002; Fig. 2); a carriage of *2 allele in the patients receiving irbesartan, was statistically significantly associated with a higher concentration of irbesartan (p <0.001). Among the patients receiving valsartan there was no statistically significant association of a steady-state drug concentration with a genotype at this locus (p=0.854).

Regarding the effect of the *CYP2C9* (*Ile359Leu*) genotype, a difference in the concentration was also found out between irbesartan and valsartan (p <0.001; Fig. 3). The carriage of allele *3 (33 patients) in the patients receiving irbesartan was statistically significantly associated with a higher concentration of irbesartan (p <0.001). Among the patients receiving valsartan there was no statistically significant association of the steady-state drug concentration with a genotype at this locus (p=0.854).

There was a trend towards an association between the genotype at the *AGTR1* (*A1166C*) locus and the steady-state concentration achieved with irbesartan and valsartan (p=0.086; Fig. 4). No statistically significant association of this polymorphic site with the irbesartan concentration was found out (p=0.55). The heterozygotes at this locus taking valsartan were characterized by a statistically significantly lower drug concentration compared to AA (p=0.001) and CC (p=0.032) homozygotes.

The effect of the *AGT* (*Met235Thr C4072T*) genotype on the steady-state concentration was statistically significantly different between the patients receiving irbesartan and valsartan (p=0.001; Fig. 5). The use of irbesartan by the TT homozygotes was associated with a higher steady-state concentration compared to the heterozygotes (p=0.019) and TT homozygotes (p=0.017), the group of patients receiving valsartan showed a trend towards a lower concentration in the TT homozygotes compared to the heterozygotes and CC homozygotes (p=0.058).

The genotype of the *ACE* polymorphic locus had a different effect on the steady-state concentrations of irbesartan and valsartan (p=0.003; Fig. 6). The D/D homozygotes receiving irbesartan showed a statistically significantly lower drug concentration compared to I/I homozygotes (p=0.013), the other pairwise comparisons showed no statistically significant differences (p=0.176). Among the patients receiving valsartan, the lowest concentration was characterized by the homozygotes

I/I and heterozygotes, with differences being statistically significant when comparing the drugs concentration between the homozygotes D/D and heterozygotes (p=0.024).

There was a tendency to the association between the steady-state concentration of the studied sartans and the *CYP11B2* (*C344T*) genotype, and the association was statistically significantly dependent on the drug (p=0.007; Fig. 7). The heterozygotes taking irbesartan were characterized by the highest concentration of the drug, the lowest concentration of valsartan was found out in the CC homozygotes, and the highest — in the TT homozygotes.

Table 3 shows the results of changes in the office SBP, DBP and HR during the therapy and the minimum steady-state drug concentration.

The patients receiving irbesartan showed statistically significantly greater reductions in the office SBP and DBP (a mean of 1.26 [95% CI: -1.51; -1] mmHg and 0.86 [95% CI: -1.16; -0.55] mmHg for every 100 ng/mL increase) at the interim assessment. No statistically significant association of these parameters with a valsartan concentration was found out. However, among the patients receiving valsartan at the interim assessment, a statistically significantly less pronounced decrease in the office HR was found out with a mean of 0.25 [95% CI: 0; 0.5] bpm for every 100 ng/mL increase in the concentration. When assessed at the end of the study, an increase in the irbesartan concentration for every 100 ng/mL was associated with a mean of 0.25 [95% CI: -0.14; 0.64] mmHg less than the pronounced decrease in the office DBP; an increase in the valsartan concentration for every 100 ng/mL was statistically significantly associated with a smaller decrease in the office SBP by a mean of 0.41 [95% CI: 0.02; 0.79] mmHg and the office HR — by a mean of 0.38 [95% CI: 0.21; 0.55] bpm.

In a single-factor regression analysis, an increase in irbesartan and valsartan concentrations for every 100 ng/mL was associated with a mean of 1.21 [95% CI: 1.08; 1.37] fold (p=0.001) and 1.3 [95% CI: 1.16; 1.46] (p <0.001) fold increase in the odds of achieving the target BP numbers at the interim study (Fig. 8), and a reduced need for the intensification of therapy (OR=0.51 [95% CI: 0.36; 0.7] and 0.78 [95% CI: 0.7; 0.88] (p *<0.001* respectively; Fig. 9). At the end of the study, there was an inverse association between the irbesartan concentration and the odds of the achieving target BP (OR=0.64 [95% CI: 0.42; 0.99] (p=0.043). No statistically significant association was found among the patients receiving valsartan (OR=0.96 [95% CI: 0.79; 1.16], p=0.651) (Fig. 10). As among the patients receiving irbesartan there was also a statistically significant association of the steady-state concentration with increased odds of the developing arterial hypotension (OR=1.72 [95% CI: 1.15; 2.56], p=0.008), the association was not statistically significant with valsartan (OR=1.05 [95% CI: 0.86; 1.27], p=0.651) (Fig. 11).

DISCUSSION

Currently, the number of studies investigating the association of genetic polymorphisms and the ARBs plasma concentration and its possible effects, is limited by a number of genetic polymorphisms studied, the sample size, and race.

In one of the first studies on the relationship between the concentration of an antihypertensive drug and its efficacy depending on the genotype, L. Kurland et al. [23] found out a relationship between the concentration of irbesartan in plasma and the dynamics of the BP reduction in the patients' homozygous T/T for the genetic polymorphism *C5245T* of the *AGTR1* gene. The study included 42 patients with hypertension of stages 1–2 and left ventricular hypertrophy, who were prescribed irbesartan 150 mg as monotherapy for 12 weeks. They were measured BP and the irbesartan concentration in its minimum value (24 h after the last dose), determined the genotype by five genetic polymorphisms of the *AGTR1* gene. The authors obtained the following results: neither an irbesartan concentration nor the genetic polymorphisms were associated with a BP response to the irbesartan treatment. However, there was an interaction between the plasma irbesartan concentration and the *AGTR1 C5245T* gene polymorphism with a decreased SBP (p=0.025). The irbesartan concentration was associated with an SBP change in the T/T homozygotes of the *AGTR1 C5245T* gene — r=-0.56, p=0.03).

In the study conducted in China by G. Chen et al. [24], the effect of the genetic polymorphism *CYP2C9* on the plasma concentration of irbesartan 30 min, 2 and 6 h after the administration, and the pharmacodynamic efficacy of irbesartan, were analyzed. A total of 196 patients participated in the study. The authors obtained the following results: the patients with the *CYP2C9*1 / CYP2C9*3* genotype had significantly higher plasma concentrations of irbesartan compared to the *CYP2C9*1 / CYP2C9*1* genotype (beta±SE=81±36) and a more pronounced DBP response (beta±SE=5.6±2.5 mmHg) at the 6 h time point, which correlates with the authors' findings. The authors concluded that the *CYP2C9*3* gene variant significantly alters the plasma concentration and the DBP response at the 6 h time point after the irbesartan treatment in the Chinese patients with hypertension.

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Table 1 – Minimum steady-state concentration of irbesartan and valsartan depending on the pharmacotherapy regimen, ng/mL, Me (Q1-Q3)

All patients (*n*=179)	Monotherapy (*n*=40)	Combination therapy (*n*=139)	*p*
Irbesartan			
2007 (1732–2554)	2438 (1990–2672)	1776 (1680–2293)	<0.001
Valsartan			
1163 (727–1537)	1504 (1428–1580)	1048 (688–1529)	0.011

Table 2 – Minimum steady-state concentration of irbesartan and valsartan according to *CYP2C9* (*Arg144Cys*), *CYP2C9* (*Ile359Leu*), *AGTR1* (*A1166C*), *AGT* (*C4072T*), *ACE* (I/D polymorphism), *CYP11B2* (*C-344T*) genotype, ng/mL, Me (Q1-Q3)

Gen	Genotypes	Irbesartan, ng/mL	Valsartan, ng/mL
CYP2C9 (*Arg144Cys*)	*1/*1	1856 (1684–2303)	1231 (688–1562)
	*1/*2 | *2/*2	2557 (2472–2630)	1095 (776–1327)
p	–	<0.001	0.854
CYP2C9 (*Ile359Leu*)	*1/*1	1914 (1690–2346)	1095 (586–1580)
	*1/*3	2798 (2689–2950)	1231 (1002–1355)
p	–	<0,001	0.854
AGTR1 (*A1166C*)	AA	2049 (1745–2573)	1428 (740–1580)
	AC	1914 (1720–2488)	776 (505–1355)
	CC	1982 (1693–2508)	1315 (1002–1629)
p	–	0.55	<0.001
AGT (*C4072T*)	CC	1788 (1633–2341)	1380 (1172–1568)
	CT	1909 (1707–2346)	1095 (740–1428)
	TT	2476 (1969–2672)	688 (519–1562)
p	–	0.009	0.058
ACE (*I/D* polymorphism)	I/I	2346 (1973–2616)	1095 (746–1580)
	I/D	2007 (1682–2559)	1002 (519–1428)
	D/D	1789 (1690–2026)	1492 (740–1685)
p	–	0.016	0.03
CYP11B2 (*C-344T*)	CC	1945 (1747–2410)	889 (688–1428)
	CT	2229 (1755–2629)	1231 (505–1629)
	TT	1830 (1655–2307)	1355 (994–1580)
p	–	0.055	0.072

Table 3 – Results of correlation analysis of changes in SBP, DBP and HR during therapy and minimum steady-state drugs concentration

Index	Irbesartan	Valsartan
3 weeks of pharmacotherapy		
Δ office SBP	-0.65 [-0.76; -0.51]; *p* <0.001	-0.08 [-0.27; 0.13]; *p*=0.465
Δ office DBP	-0.48 [-0.63; -0.29]; *p* <0.001	-0.14 [-0.33; 0.06]; *p*=0.181
Δ office HR	0.02 [-0.19; 0.24]; *p*=0.846	0.21 [0.01; 0.4]; *p*=0.036
3 months of pharmacotherapy		
Δ office SBP	0.18 [-0.04; 0.38]; *p*=0.115	0.25 [0.05; 0.43]; *p*=0.013
Δ office DBP	0.22 [0.01; 0.42]; *p*=0.045	0.1 [-0.1; 0.3]; *p*=0.312
Δ office HR	0.18 [-0.04; 0.38]; *p*=0.111	0.47 [0.3; 0.61]; *p* <0.001

Note: SBP — systolic blood pressure; DBP — diastolic blood pressure; HR — heart rate.

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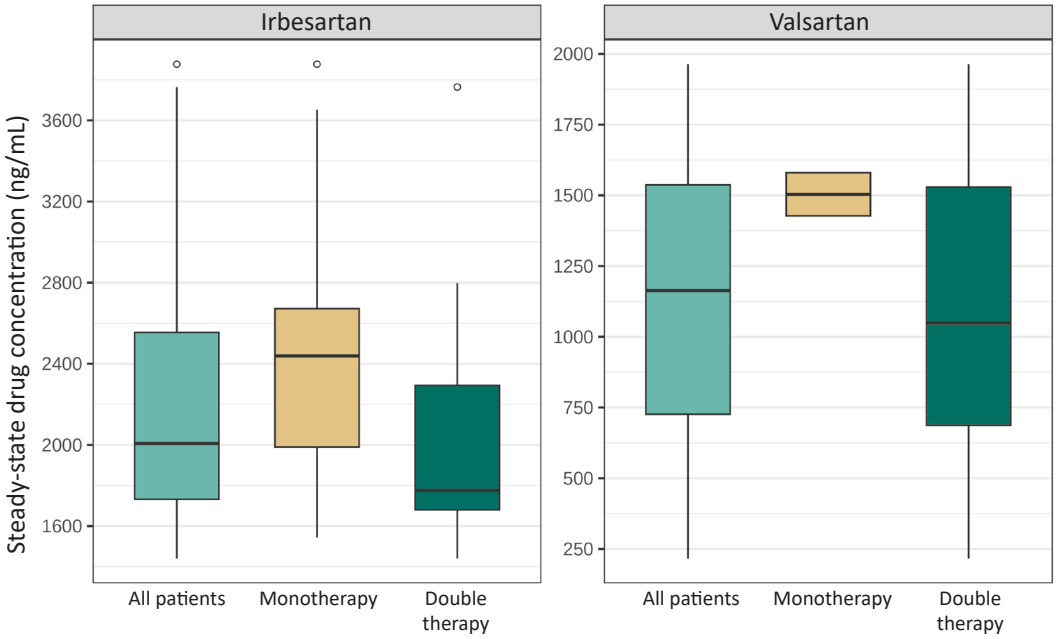

Figure 1 – Minimum steady-state concentration of irbesartan and valsartan depending on the pharmacotherapy regimen.

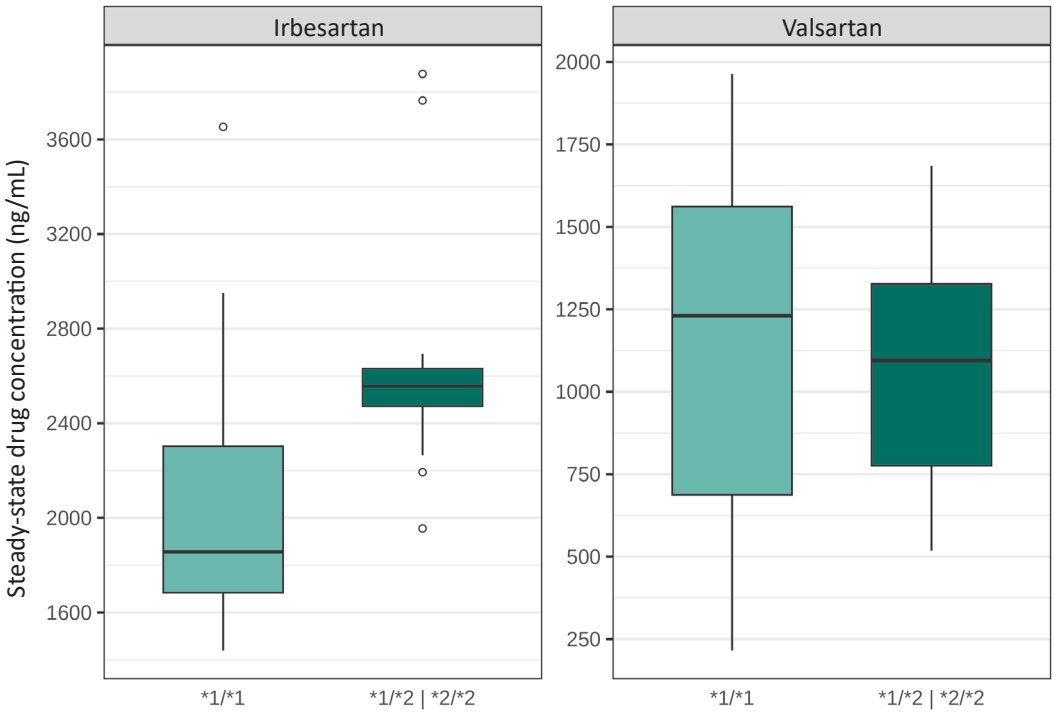

Figure 2 – Minimum steady-state drugs concentration depending on *CYP2C9* genotype (*Arg144Cys*) in irbesartan and valsartan patient groups.

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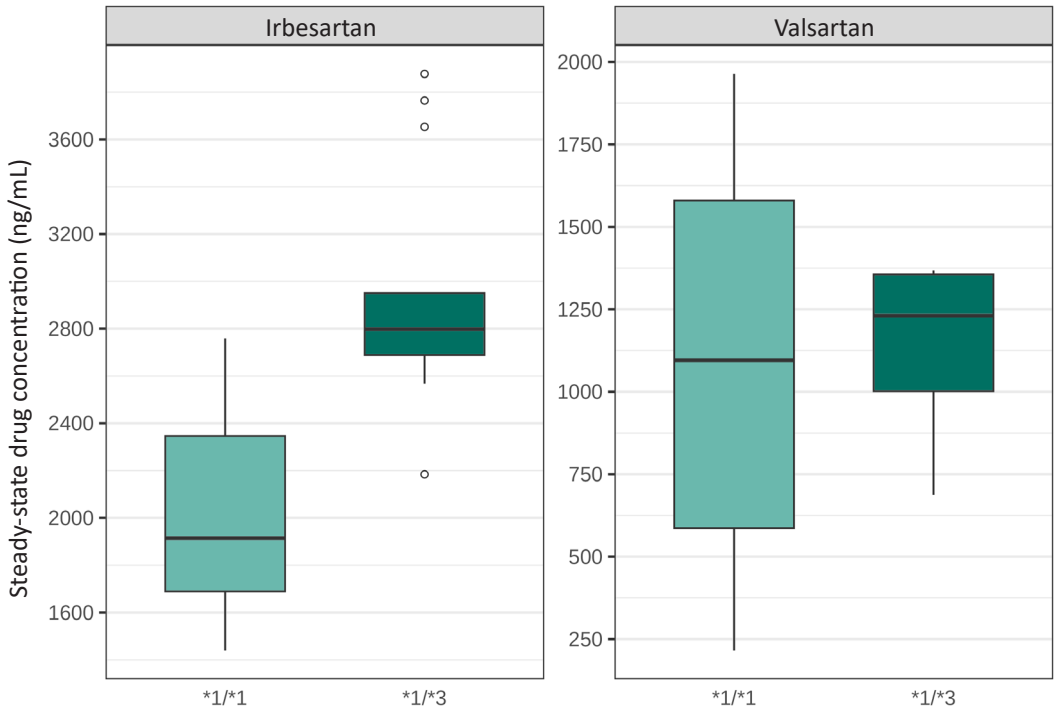

Figure 3 – Minimum steady-state drugs concentration depending on *CYP2C9* genotype (*Ile359Leu*) in irbesartan and valsartan patient groups.

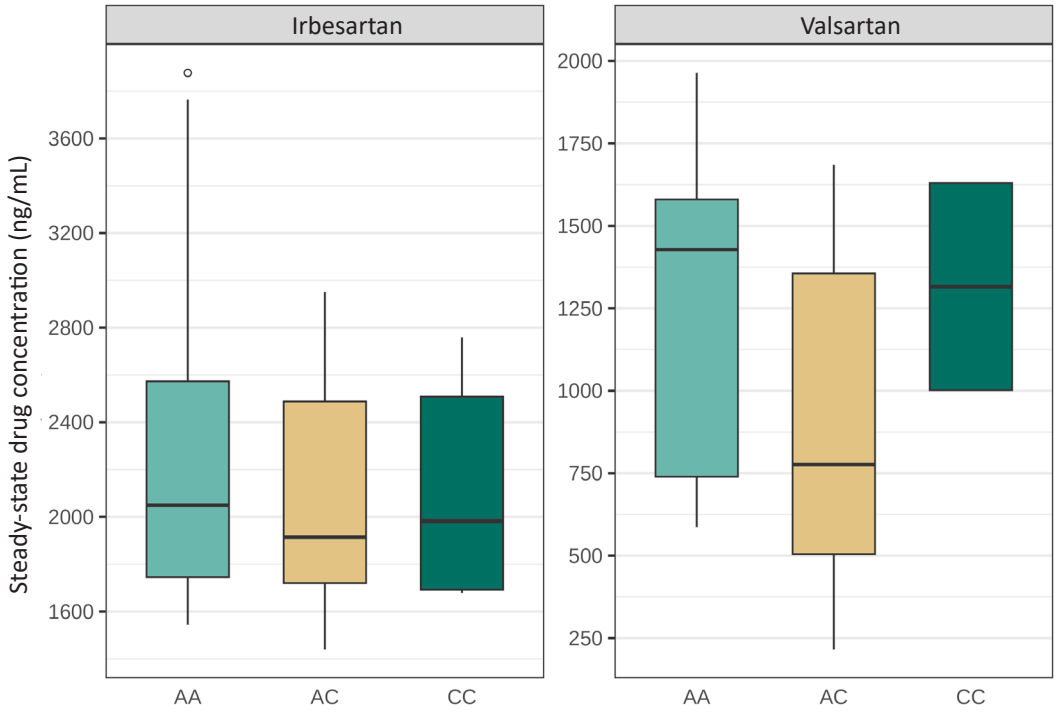

Figure 4 – Minimum steady-state drugs concentrations depending on *AGTR1* genotype (*A1166C*) in irbesartan and valsartan patient groups.

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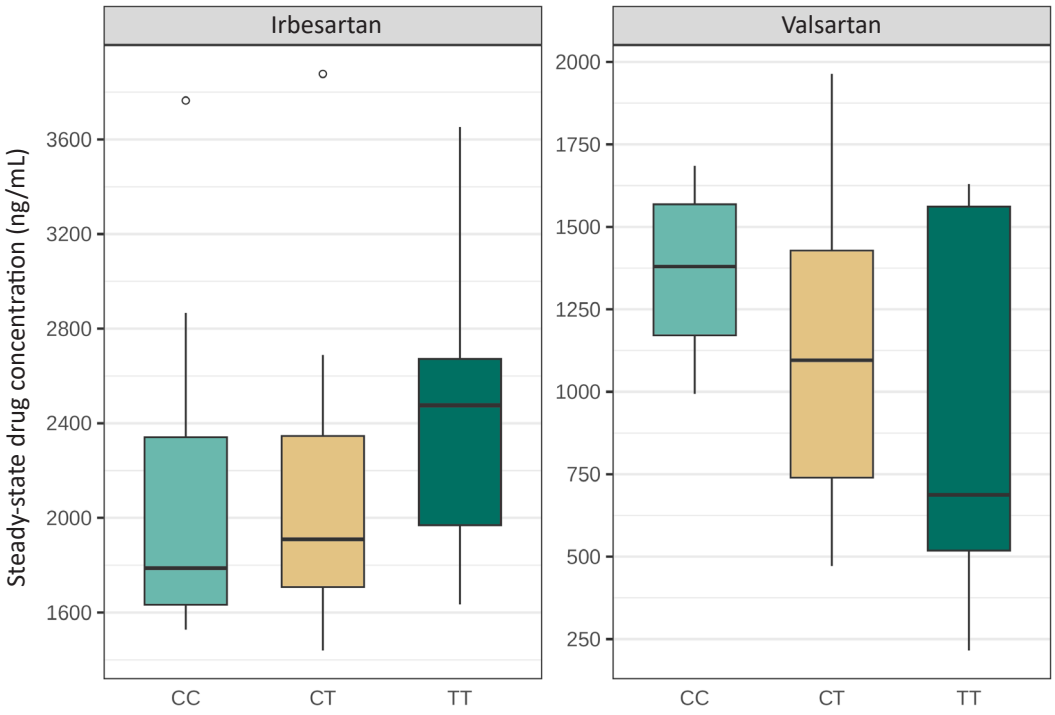

Figure 5 – Minimum steady-state drugs concentrations depending on *AGT* genotype (*C4072T*) in irbesartan and valsartan patient groups.

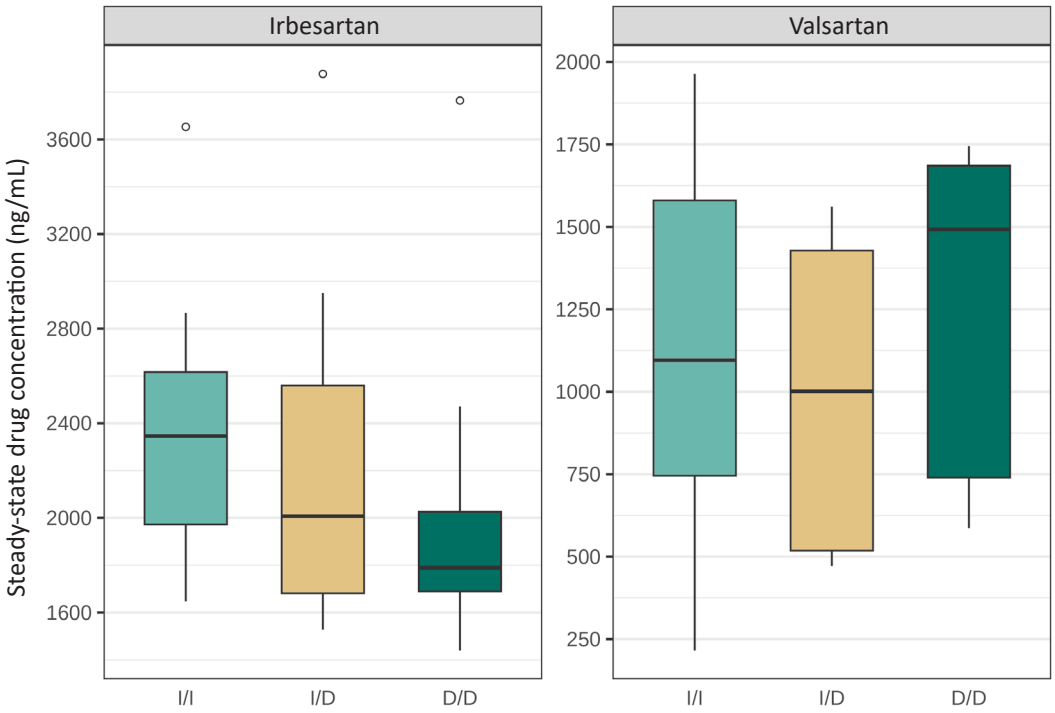

Figure 6 – Minimum steady-state drugs concentration depending on *ACE* genotype (*I/D* polymorphism) in irbesartan and valsartan patient groups.

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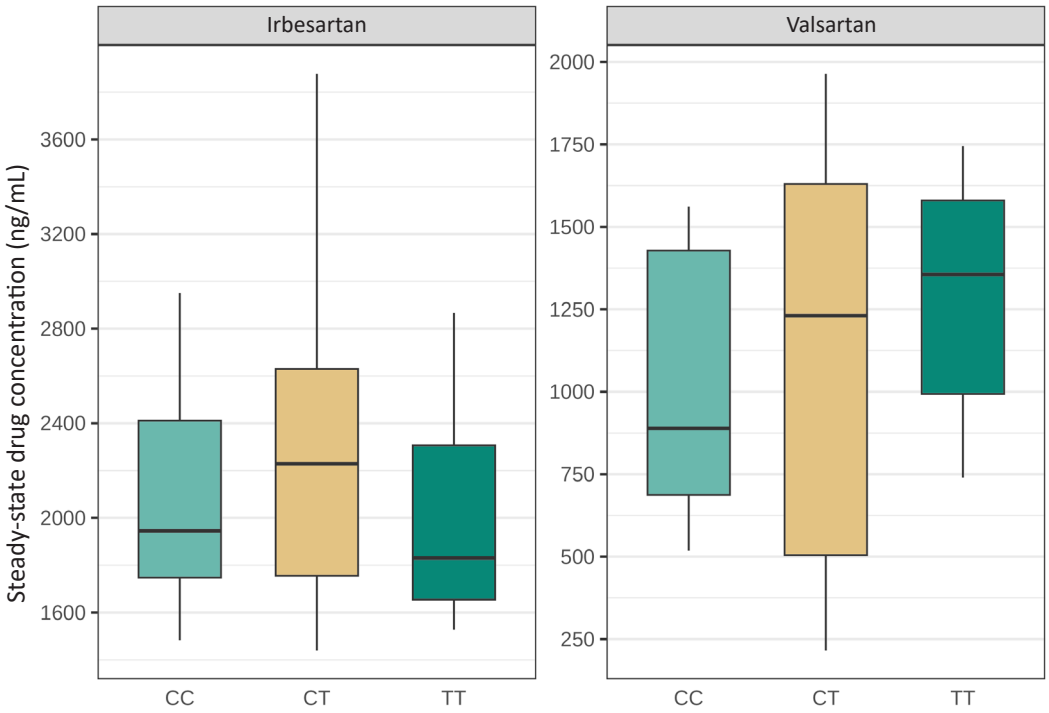

Figure 7 – Minimum steady-state drugs concentration depending on *CYP11B2* genotype (*C-344T*) in irbesartan and valsartan patient groups.

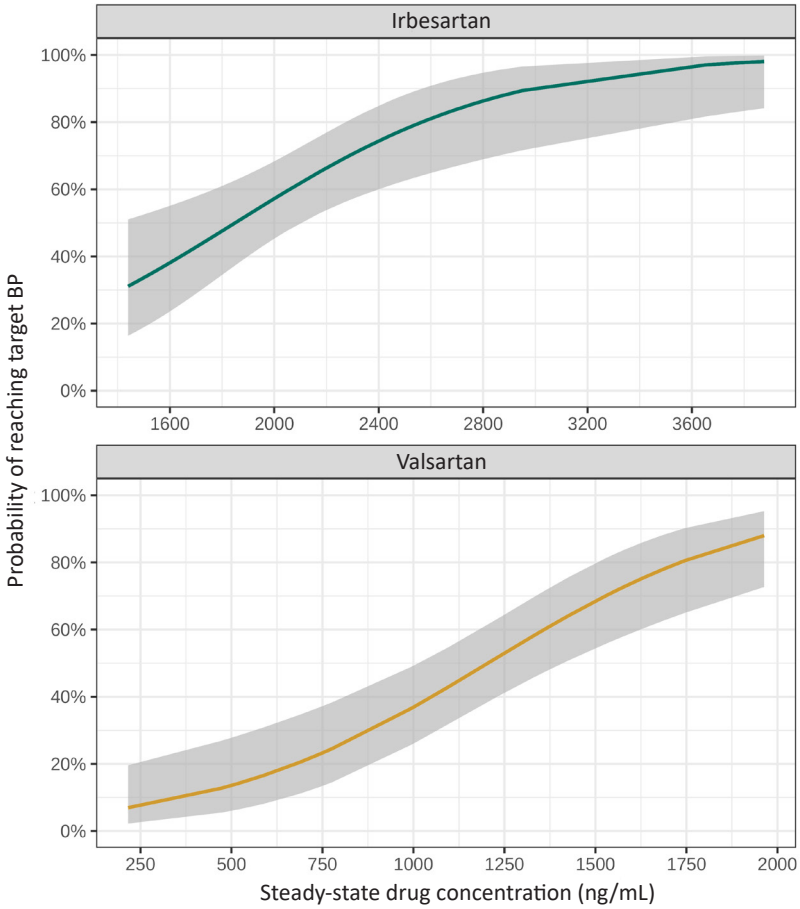

Figure 8 – Probability of achieving the target blood presure at the intermediate stage as a function of the minimum steady-state drugs concentration.

Note: BP — blood pressure.

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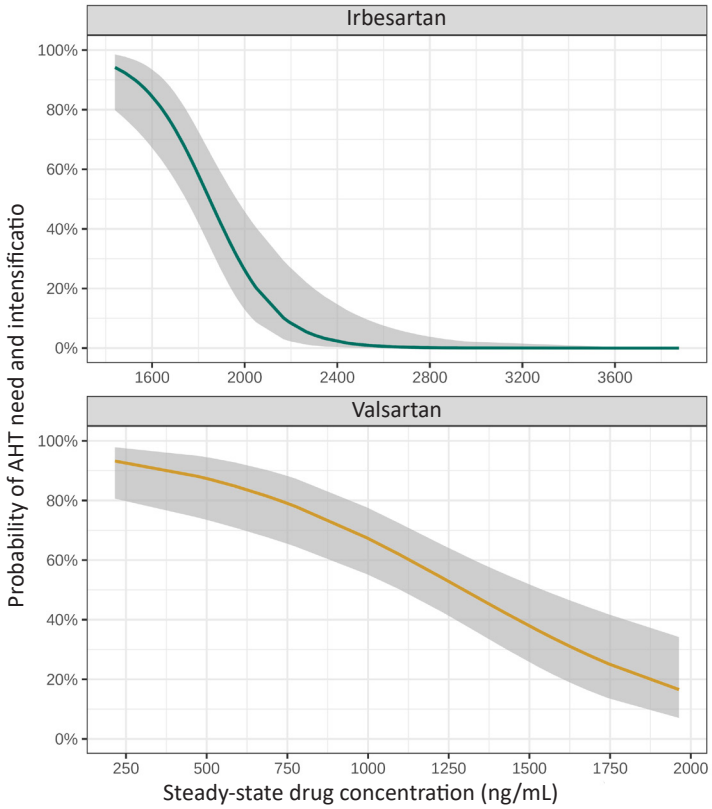

Figure 9 – Probability of need and intensification of antihypertensive therapy depending on the minimum steady-state drugs concentration.

Note: AHT — antihypertensive therapy.

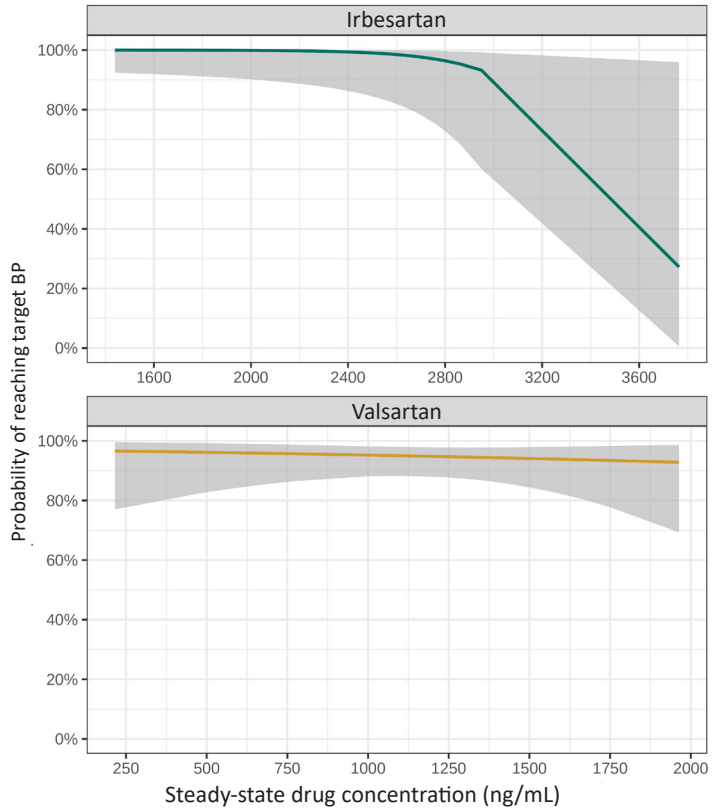

Figure 10 –Probability of achieving the target blood pressure at the end of the study depending on the minimum steady-state drugs concentration.

Note: BP — blood pressure.

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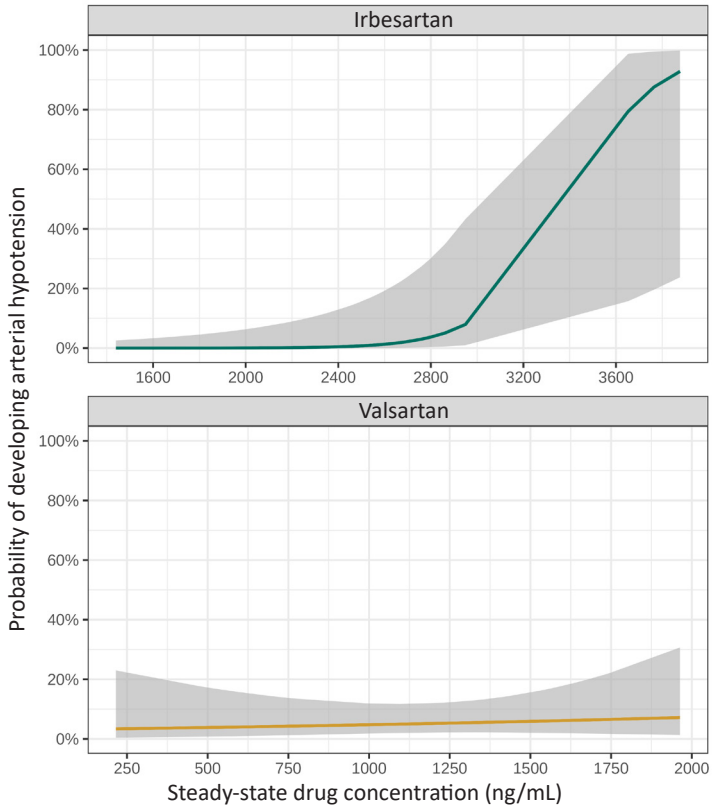

Figure 11 – Probability of developing arterial hypotension depending on the minimum steady-state drugs concentration.

In the study by S. Zhang et al. [25], the association between the *ANP Val7Met* polymorphism (a single nucleotide polymorphism database identifier — rs5063) and a baseline BP, the minimum steady-state plasma concentration of irbesartan and the antihypertensive efficacy of irbesartan, were studied in the AH patients in the Chinese population. A total of 756 patients were included in the study. The authors found no significant association between the antihypertensive efficacy and the *Val7Met* polymorphism in the overall population. But when analyzed by the baseline DBP level, the patients with the Val / Met+Met / Met genotype and the baseline DBP greater than or equal to 100 mmHg, had a significantly smaller reduction in DBP (the adjusted regression coefficient -5.7 [1.4] mmHg; $p < 0.001$) and SBP compared with the patients with the Val / Val genotype and the baseline DBP greater than or equal to 100 mmHg (the adjusted regression coefficient -9.8 [2.9] mmHg; $p<0.001$). Thus, the authors concluded that in the AH patients living in China, the *ANP Val7Met* polymorphism could be a genetic marker of the baseline DBP, the plasma irbesartan concentration and the antihypertensive efficacy of a short-term irbesartan therapy.

In the study by S. Hu et al. [26], the relationship of the kininogen gene (*KNG1*) polymorphism *Ile197Met* and the gender was investigated in the hypertension patients' plasma with the concentration of irbesartan. The study enrolled 1 100 patients. The authors determined that the male patients carrying the G allele had significantly lower plasma concentrations (GG — p=0.015; TG — p=0.015, respectively) compared with the TT genotype, and concluded that the interaction of the gender and the *KNG1 Ile197Met* polymorphism could influence the plasma concentration of irbesartan, which can contribute to a better development of a personalized hypertension treatment in Chinese patients.

According to the results of the study, in the course of a comparative analysis, the differences were established with regard to the influence of a genotype according to the studied genetic polymorphisms, both in the group of patients taking irbesartan and valsartan, on the values of the minimum steady-state ARBs concentration.

Thus, among the patients taking irbesartan, the figures of the minimum steady-state concentration were significantly higher in the carriers of allele *2 for the genetic polymorphism of the *CYP2C9* gene (*Arg144Cys*), the carriers of allele *3 for the genetic polymorphism of the *CYP2C9* gene (*Ile359Leu*), in T/T homozygotes for the genetic polymorphism of the *AGT* gene (*Met235Thr*, *C4072T*), in the homozygotes I/I by the I/D polymorphism

of the *ACE* gene, and there was also a tendency for an association between the minimum steady-state concentration and the genotype by the genetic polymorphisms of the *AGTR1 (A1166C)* and *CYP11B2 (C-344T)* genes — higher values of the minimum steady-state concentration were observed in the homozygotes A/A and heterozygotes C/T, respectively. Herewith, the patients in the irbesartan group showed a significantly more pronounced decrease in the office SBP and DBP at an increase in the concentration for every 100 ng/mL after three weeks of the drug administration compared to the group of the valsartan patients, and after 3 months of therapy with irbesartan, there was a statistically significant less pronounced decrease in the office DBP for every 100 ng/mL. Increasing the plasma concentration of irbesartan for every 100 ng/mL was associated with a mean of 1.21 [95% CI: 1.08; 1.37] fold increase in the odds of achieving the target BP numbers after 3 weeks of therapy (p=0.001) and a corresponding decrease in the need for the intensification of therapy (OR=0.51 [95% CI: 0.36; 0.7] (p<0.001).

Among the patients taking valsartan, the figures of the minimum steady-state concentration were significantly higher in the A/A homozygotes for the *AGTR1* gene polymorphism (*A1166C*), in the D/D homozygotes for the I/D polymorphism of the *ACE* gene, and there was also a tendency to the presence of a relationship between the minimum steady-state concentration of valsartan and the genotype of the genetic polymorphism of the *AGT* gene (*Met235Thr*, *C4072T*) — higher values were determined in the C/C homozygotes. Herewith, no statistically significant associations with the office SBP and DBP were found when increasing the minimum steady-state concentration by every 100 ng/mL when assessed after 3 weeks of pharmacotherapy. When analyzed after 3 months of the valsartan therapy, an increase in the concentration for every 100 ng/mL was significantly associated with a smaller decrease in the office SBP and a less pronounced decrease in the night SBP variability. Increasing the valsartan plasma concentration by every 100 ng/mL was associated with a mean of 1.3 [95% CI: 1.16; 1.46] fold increase in the odds of achieving the target BP after 3 weeks of therapy (p <0.001) and a corresponding decrease in the need for the intensification of therapy (OR=0.78 [95% CI: 0.7; 0.88] (p <0.001).

Study limitations

One of these study limitations is a relatively small sample size and a separate region of the study. A promising avenue for further research is to identify predictors of response to the antihypertensive therapy, including age, renin levels, and genetic polymorphisms affecting the pharmacodynamics and pharmacokinetics of the antihypertensive drugs, as these factors may have a significant impact on the efficacy and safety of the treatment.

A detailed analysis of an individual sensitivity of patients to different classes of antihypertensive drugs will allow the development of personalized approaches to the choice of starting therapy, which may improve the effectiveness of a BP control and reduce the risk of adverse reactions.

CONCLUSION

Patients with newly diagnosed hypertension of stages 1–2, of the Moscow region, the carriers of alleles *2 and *3 of the *CYP2C9* gene, the genotype T/T of the *AGT* gene, the genotype I/I by the I/D-polymorphism of the *ACE* gene achieved significantly higher values of the minimum steady-state irbesartan concentration after 3 weeks of pharmacotherapy. The patients with newly diagnosed newly diagnosed hypertension of stages 1–2 of the Moscow region homozygotes A/A for the genetic polymorphism of the *AGTR1* gene (*A1166C*), the homozygotes D/D for the I/D polymorphism of the *ACE* gene achieved significantly higher values of the minimum steady-state valsartan concentration after 3 weeks of pharmacotherapy.

In the patients on the ARBs monotherapy, the values of the minimum steady-state irbesartan and valsartan concentrations were significantly higher compared to the patients on the combination therapy with hydrochlorthiazide.

The obtained irbesartan and valsartan effects indicate a maximal modulation of pharmacodynamic effects during 3 weeks of pharmacotherapy with a subsequent consolidation in the therapeutic range and stopping in the increase of the efficacy with a further increase of the steady-state concentration, which can be used for a pharmacokinetic therapy prediction, its personalization, a better control and a high safety profile.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

Ekaterina V. Rebrova — concept development, conducting the study, preparation and editing the text, approval of the final version; Evgenia V. Shikh — concept development, conducting the study, preparation and editing the text, approval of the final version; George S. Anikin — conducting the study; Valery V. Smirnov — conducting the study, resource support of the study; Maxim M. Bogdanov — conducting the study; Ludmila M. Ignatova — conducting the study.

All the authors confirm that their authorship meets the international ICMJE criteria (all the authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before the publication).

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