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PHARMACOGENOMIC STRATEGY FOR SELECTION OF HYPOTENSIVE DRUGS AND PROSPECTS FOR ITS USE IN PREGNANT WOMEN

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Summary

Cardiovascular disease (CVD) is one of the leading causes of death worldwide, and arterial hypertension (AH) is the strongest risk factor for its development. The problem of hypertension is also relevant during pregnancy, as high blood pressure can be dangerous for both the mother and the fetus, causing pre-eclampsia and premature birth. According to recent data, the number of patients with hypertension will increase. Because of the polygenic and multifactorial nature of the therapeutic response to drugs, further research in this area is needed to provide evidence-based guidelines for clinicians to optimize antihypertensive therapy.

The purpose of this review was to summarize information from scientific publications, meta-analyses, guidelines for the years 2018-2023 regarding variants in genes that affect the metabolism of different classes of drugs used in the treatment of hypertension, including during pregnancy, and related to the development of AH.

The pathogenesis of hypertension is based on both a decrease in vasodilatation and an increase in circulating blood volume. Arterial stiffness leads to a decrease in vasodilation, and water and sodium retention leads to an increase in blood volume. Additional factors such as the renin-angiotensin-aldosterone system, the sympathetic nervous system, and gene variants affect both vasodilation and blood volume. In addition, there are complex interactions among these factors. As an innate factor, gene variants can affect all of the above simultaneously.

The American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines recommend the use of medications from the following 5 classes: diuretics, calcium channel blockers (CCBs), beta-adrenergic receptor blockers (beta-blockers), angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers.

The studies included in this review used two main approaches: candidate gene analysis and genome-wide association analysis. The polygenic nature of hypertension greatly complicates the search for clinically relevant variants and relationships between individual genes and response to medications used to treat hypertension in different ethnic groups.

Candidate genes that may influence the risk of hypertension include voltage-dependent calcium channel genes (CACNA1A, CACNA1C, CACNA1S, and CACNB2), NEDD4L, ADD1, and miR. A number of genetic polymorphisms are associated with both the influence on the development of arterial hypertension and the response to treatment – eNOS, TRIB3, CYP, POR, ADRB1, ADRB2, ACE. When treating pregnant women with hypertension, the efficacy of the antihypertensive agent must be balanced against the risk to the fetus. Initial antihypertensive therapy should include an acceptable first-line agent.

The development of a pharmacogenomic strategy to select the most effective and well tolerated drug treatment regimen for hypertension is of paramount importance, as it will lead to a lower number of drugs required per patient and better blood pressure control, help prevent cardiovascular and renal complications, and improve quality and length of life.

Key words: *Arterial Hypertension; Risk Genes for Arterial Hypertension; Pharmacogenetics of Hypotensive Drugs; Pregnant Women.*

Relevance of the topic

Cardiovascular disease (CVD) is a leading cause of death worldwide, and arterial hypertension (AH) is one of the strongest risk factors for its development [1]. The problem of hypertension is also relevant during pregnancy, as high blood pressure can be dangerous for both the mother and the fetus, causing pre-eclampsia and preterm delivery. According to the latest data, the number of patients with hypertension will increase and by 2025 it will be observed in about 1.5 billion people, but a large number of cases of hypertension remain undiagnosed [2]. Therefore, improving the clinical effectiveness of hypertension control through pharmacogenetic testing is desirable and important. This is supported by a large-scale study by Xiao et al, which showed that personalized treatment of patients with AH based on pharmacogenetic testing is a more effective strategy [3].

Previously, hypertension was defined as a blood pressure greater than 140 mm Hg (systolic, SBP) and greater than 90 mm Hg (diastolic, DBP), but current recommendations have changed the values to 130 and 80 mmHg, respectively. Heart rate (HR) should be within 72 beats/min [4]. Hypertension has no symptoms, but it destroys blood vessels over time, which is why it is often called the «silent killer». The rate of undiagnosed and uncontrolled hypertension is associated with the frequent absence of its distinct clinical manifestations, low treatment efficiency and possible adverse reactions to drug components. According to the results of several genome-wide association studies (GWAS), genetic factors

are associated not only with elevated blood pressure (BP), but also with interindividual variability in response to treatment [5, 6], which is consistent with the well-known mosaic theory proposed by I. Page in 1979 and later modified [7]. Because of the multigenic nature of AH, a single locus cannot be used as a relevant clinical target for all individuals, and interactions between multiple loci need to be evaluated. After conducting several GWAS, single nucleotide polymorphisms (SNPs) have been identified that are associated with hypertension and correlated with the efficacy and adverse effects of antihypertensive drugs, but due to the polygenic and multifactorial nature of the therapeutic response to drugs, further studies in this area are needed to develop reliable recommendations for clinicians that will help optimize antihypertensive therapy [8].

The aim of this review was to summarize information from scientific publications, meta-analyses, recommendations for 2018-2023 regarding variants in genes that affect the metabolism of various classes of medications that are used in the treatment of AH, including during pregnancy, and are associated with the development of AH.

1. Molecular pathogenesis of hypertension

A mosaic theory has been proposed to explain the pathogenesis of AH, emphasizing the state of the vasculature, the level of salt intake, the activation of the sympathetic nervous system, genetic influences, the gut microbiome, renal mechanisms, the role of inflammation/immune responses, and oxidative stress [7, 9, 10].

It can be assumed that the basis of the pathogenesis of hypertension is both a decrease in vasodilatation and an increase in the volume of circulating blood. Arterial stiffness leads to a decrease in vasodilation, and water and sodium retention leads to an increase in blood volume. Additional factors such as the renin-angiotensin-aldosterone system, the sympathetic nervous system, and gene variants affect both vasodilation and blood volume. In addition, there are complex interactions among these factors. As an innate factor, gene variants can affect all of the above simultaneously [11].

2. Drugs for the treatment of hypertension

The American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines recommend the use of drugs from the following 5 classes: diuretics, calcium channel blockers (CCBs), beta-adrenergic receptor blockers (beta-blockers), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) [12, 13]. The AHA notes the superiority of the thiazide diuretic chlorthalidone over other diuretics because this drug has been used in many randomized clinical trials. Both guidelines recommend combination therapy for most adults with hypertension and do not recommend concomitant use of ACE inhibitors and ARBs.

In the ESC guidelines, β-blockers are considered first-line antihypertensive drugs in patients with specific indications for their use, because compared with other antihypertensive drugs, β-blockers are generally equivalent in the prevention of major cardiovascular disease, except for a lower efficacy in the prevention of stroke. Therefore, their use is recommended primarily for specific (mainly cardiologic) indications and in pregnant women or women planning to become pregnant [14].

CCBs are drugs that bind to and block mainly L-type calcium channels on smooth muscle cells of the heart and blood vessels [1]. They prevent calcium ions from entering the vascular smooth muscle, resulting in muscle relaxation and vasodilation, as well as a decrease in vascular resistance and, consequently, a decrease in blood pressure. The renin-angiotensin system affects blood pressure and sodium homeostasis through actions coordinated by combined mechanisms in the kidney, cardiovascular system, and central nervous system. The actions of the renin-angiotensin system are mediated by the renin-linked conversion of angiotensinogen to angiotensin I, which is further cleaved by ACE to form angiotensin II (Ang II). Ang II, the final effector of the system, stimulates angiotensin II type 1 receptors (AT1R) located in the vasculature, kidney, and central nervous system, resulting in vasoconstriction, sodium reabsorption, and increased sympathetic tone. As mentioned above, two different classes of drugs that affect the renin-angiotensin system are prescribed to control hypertension, namely ACE inhibitors, which prevent the formation of Ang II, and ARBs, which bind to the AT1R and antagonize the action of Ang II.

Diuretics, especially thiazide and thiazide-like diuretics, are the first-line treatment for most patients with hypertension [2]. The thiazide diuretic hydrochlorothiazide inhibits the sodium chloride cotransporter expressed in the distal convoluted tubule of the nephron. The initial antihypertensive effect of these drugs includes an increase in natriuresis and a decrease in extracellular volume, leading to a decrease in cardiac output. In addition, these drugs have a long-term effect due to a decrease in vascular resistance, probably as a result of suppression of the sympathetic nervous system and/or the renin-angiotensin system.

3. Study of candidate genes for the risk of AH developing

Voltage-gated calcium channels (VCCs) mediate the influx of calcium ions into cells to cause vascular smooth muscle contraction, neurotransmitter or hormone release, and gene expression. These channels are a multiprotein complex consisting of different subunits, including α1, β, α2/δ and γ. The activity of VCC is mainly controlled by the pore-forming subunit α1, which is the target of calcium channel blockers, and can be divided into different types, such as α1A, α1B, α1C, α1D, α1E. and α1S [15]. In the study by Huang et al., variants were selected from genes encoding alpha 1A (CACNA1A), alpha 1C (CACNA1C), alpha 1S (CACNA1S), and beta (CACNB2) subunits. According to the results of the above study, variants of these genes were associated with the development of hypertension, namely CACNA1S (rs2365293), CACNB2 (rs17539088), CACNB2 (rs16917217), CACNB2 (rs61839222), and CACNA1A (rs10425859), which deserve attention in future studies [15]. In another study, hypertension in Han was associated with ACE I/D and ADRB1 1165G > C gene variants [16].

NEDD4L (neuronal precursor cell expressed developmentally down-regulated gene 4-like) is

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considered a candidate gene for hypertension through regulation of ubiquitination of epithelial sodium channels. Ubiquitination is a common post-translational modification of proteins that involves the addition of ubiquitin, a small, highly conserved protein, to substrate proteins, leading to either their degradation in proteasomes or their cleavage in lysosomes. Ubiquitin is covalently attached at its C-terminus to specific lysine residues on the target protein, a process mediated by the sequential action of three types of enzymes: E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ubiquitin ligases. A study by Mohammed et al [17] identified *Nedd4-2* (encoded by the *NEDD4L* gene) as the first E3 ubiquitin ligase involved in the ubiquitination of angiotensin-converting enzyme 2 (ACE2), a critical component of the compensatory renin-angiotensin system whose activity is reduced during the development of AH. The results of this study suggest that *Nedd4-2* may promote the ubiquitination of ACE2, leading to the development of neurogenic hypertension.

Niu et al. demonstrated that the *NEDD4L* rs74408486 variant was associated with systolic and diastolic BP during a low-salt diet, while rs292449 and rs2288775 were significantly associated with the HR response to a high-salt diet [18]. In addition, in this study, rs292449 was significantly associated with the incidence of hypertension during 14 years of follow-up. In another study, the *AA* genotype (rs4149601) was associated with hypertension in Chinese patients with chronic kidney disease (CKD), so it can be assumed that the *A* allele (*rs4149601*) may be a risk factor for the development of hypertension in CKD [19]. In the study by Zhao et al. [20], European women with the *AA* genotype (rs4149601) were 80 % less likely to develop early-onset hypertension compared to carriers of the *AG* or *GG* genotypes, so it can be assumed that there is a significant correlation between the above-mentioned variant and the early onset of hypertension in Caucasian women, but further larger studies are needed.

The *ADD1* gene encodes one of the adducin subunits (α-adducin). Adducin modulates the surface expression of many transporters and ion pumps, and thus regulates cell signaling and ion transport. Studies have shown that the contribution of the *ADD1* Gly460Trp (rs4961) variant to the development of hypertension may vary in different ethnic groups, but meta-analyses have not been able to reach a consensus on this issue [21]. The *ADD1* Gly460Trp variant was recently demonstrated to be an important predictor of the development of AH in the Ukrainian population, but further studies with a larger sample of participants and consideration of other non-genetic factors are necessary [22].

Although microRNA (miRNA)-mediated functions and gene expression regulation have been implicated in cardiovascular disease susceptibility, the potential impact of miRNA variants on patients' susceptibility to hypertension remains poorly understood. A stratified analysis by Choi et al [23] showed that miR-200b T>C (rs7549819) and miR-495 A>C (rs2281611) polymorphisms were associated with the risk of hypertension, with differences in the levels of body mass index, fasting blood glucose, high-density lipoprotein (HDL), and systolic blood pressure. Data from this study suggest that the miR-495A>C variant and allelic combinations (miR-200bT>C/miR-495A>C haplotype) may increase susceptibility to hypertension in the Korean population.

4. Candidate genes associated with the risk of developing hypertension and response to treatment

4.1 Endothelial nitric oxide synthase (eNOS)

It is known that eNOS plays a crucial role in the regulation of vascular tone and blood pressure [24]. In addition, it has been found that inhibition of the NOS3 gene in healthy individuals is associated with a decrease in NO release and an increase in blood pressure [25]. The NOS3 gene, located on chromosome 7q35-36, contains 26 exons and 25 introns. There are about 10 polymorphic loci distributed in the promoter, exon and intron of this gene. In these loci, the most common mutation leading to amino acid substitutions in mature proteins is the G894T (or Glu298Asp rs1799983) variant, in which a G to T substitution results in the replacement of glutamic acid in exon 7 by aspartic acid at position 298 of the corresponding amino acid [25]. A decrease in the concentration of NO produced by eNOS catalysis is associated with a higher level of BP and may be a consequence of the presence of the listed genetic variants and their contribution to endothelial dysfunction and vasopressor effect, hyperplasia and hypertrophy of smooth muscle cells, affecting the development of essential AH.

Shi et al. [25] found that the *NOS3* polymorphism (rs1799983) was associated with an increased risk of hypertension in any genetic model, but further studies are needed to better understand the relationship between the *eNOS* gene variants and AH. Another group of scientists in their cross-sectional study also found that the T allele of the rs1799983 variant is associated with hypertension in Brazilian women [26]. Another confirmation was obtained by Isordia-Salas et al. determined that the rs1799983 variant and the T allele were positively associated with the risk of developing essential hypertension in the Mexican population [27].

Some CCBs, such as nifedipine, have demonstrated effects on NO bioavailability [28]. Also, according to data from literary sources, amlodipine can determine vasodilation by activating eNOS [28]. This drug blocks the outflow of calcium, deactivating eNOS by regulating the concentration of Ca^{2+}. In the large-scale GenHAT study for carriers of rs1799983 and rs3918226, the advantage of using amlodipine compared to lisinopril was demonstrated [29]. The authors also recorded an association between *eNOS* variants and coronary heart disease (CHT), heart failure and stroke, which may help guide drug selection in the future.

It is well known that plasma levels of nitrates, nitrates and nitrites increase during treatment with ACE inhibitors and ARBs [30]. Increased NO release during ARB therapy can be explained by reduced Ang II activity leading to increased antioxidant defense and NO bioavailability. It has been shown that olmesartan can increase NO levels by approximately 30 % in homozygotes CC for the T-786C variant (rs2070744) compared to heterozygotes, and carriers of the C allele may have a better response to

enalapril and olmesartan [1]. In general, the heterozygous TC (rs2070744) genotype is more common in those who respond well to enalapril treatment than in those who respond poorly [2].

2.2 TRIB3 gene

TRIB3 (tribbles pseudokinase 3) is a cytosolic protein that binds to protein kinase B (or AKT) and inhibits its functional activity. It is necessary to remind that protein kinase B is the main mediator of insulin signaling processes, which is a key regulator of blood glucose levels in the body. Therefore, TRIB3 plays an important role in various cellular processes, such as glucose metabolism, apoptosis, cell proliferation, etc.

Accumulating results from numerous studies indicate that some drugs or active substances affect vascular function by regulating the *TRIB3* gene. Thus, homocysteine, which is largely associated with hypertension, can increase the expression of the *TRIB3* gene, which leads to endothelial dysfunction [31].

One of the most studied is the missense variant rs2295490 (251A>G, Gln84Arg or Q84R) in exon 2 of the *TRIB3* gene, where the 84Arg allele is a stronger inhibitor of AKT compared to the more frequent 84Gln allele. It was shown that carriers of the AA genotype had a better antihypertensive effect than carriers of the AG and GG genotypes after treatment with CCBs such as azelnidipine and nitrendipine [31]. In the same study, carriers of the AG and GG genotypes of the *TRIB3* gene benefited more from antihypertensive ARB therapy.

For other options – He et al. demonstrated that carriers of the CC genotype for the rs6037475 variant of the *TRIB3* gene had significantly higher BP and SBP than carriers of the TT genotype during felodipine therapy [32].

4.3 Cytochrome P450 genes

Cytochromes P450 (CYP) are the family of heme-containing enzymes that have an oxidation function and play an important role in the metabolism of many endogenous and exogenous compounds.

Cytochrome P450 family 3 subfamily A (CYP3A) enzymes are largely responsible for drug metabolism in adults, including the disposition of antihypertensive drugs. The prevalence of CYP3A4 and CYP3A5 gene variants has been shown to differ among different ethnic groups and may account for much of the observed variability in drug efficacy and toxicity.

Depending on the studied population, it has been shown that *CYP3A4/5* carriers exhibit ethnic and gender differences that may affect the effectiveness of such ARB as amlodipine [33]. In particular, variants rs2246709 and rs2740574 of the *CYP3A4* gene were associated with a better BP response to amlodipine in the African-American population, while the variant rs776746 of the *CYP3A5* gene was associated with a better response to treatment with this drug in Korean and Chinese patients. In a study by Liang et al. in Chinese patients with hypertension who are carriers of genotypes CC and AA, respectively, variants rs776746 and rs15524 of the *CYP3A5* gene demonstrated an increased risk of amlodipine-induced peripheral edema [34]. On the contrary, in patients who are carriers of AC and AA genotypes according to the variant rs4646453 of the *CYP3A5* gene, a reduced risk of such peripheral edema was recorded.

Among healthy Chinese subjects, in the group of wild-type carriers, such a pharmacokinetic parameter as the area under the «plasma concentration-time» curve from the moment of taking tileridipine to 24 hours (AUC0-24) was 1.35 times greater than in carriers of the CYP3A4*1G allele by variant rs2242480 of the CYP3A4 gene [35]. Among the three genotypes according to the variant rs776746 (or CYP3A5*3) of the *CYP3A5* gene in the mentioned study, a significant difference was found only in the half-life of tileridipine. Thus, in subjects with the CYP3A5*3/*3 genotype, the average half-life of tileridipine was higher than in subjects with the CYP3A5*1/*1 genotype [35]. The above suggests that CYP3A4*1G and CYP3A5*3 variants may affect the pharmacokinetics of tileridipine.

In the Han ethnic group (China), a high frequency of the rs776746 variant of the CYP3A5 gene was determined, which may indicate that they are more sensitive to β-blockers and CCB [16]. A study by Lee et al. found that the *CYP3A5*3* polymorphism was not associated with adverse reactions to ARBs in patients with CKD [36].

A study by Chan et al [37] found that *CYP2D6* and *CYP3A5* variants were apparently not useful for predicting the hemodynamic response to bisoprolol in Chinese patients with hypertension. However, in another study – in patients from Saudi Arabia – the association of the variant rs1080985 (–1584C>G or 1496C>G) of the *CYP2D6* gene with the concentration of bisoprolol in plasma was demonstrated [38]. In the mentioned study, the plasma concentration of bisoprolol in CC genotype carriers was significantly lower than in CG and GG carriers, and CC genotype carriers also had higher SBP and DBP. Therefore, the authors suggested that there is a window for increasing the dose of bisoprolol for patients with the CC genotype for the rs1080985 variant of the *CYP2D6* gene.

In another meta-analysis, carriers of CYP2C9*2 or *3 variants, compared to wild-type carriers, showed a larger area under the plasma concentration-time curve in the interval 0-∞ (AUC0-∞) for losartan and a smaller AUC0-∞ for E-3174, the active metabolite of losartan [39]. Also, carriers of CYP2C9*2 or *3 variants showed a lower maximum concentration of E-3174 and had a longer half-life of losartan and E-3174.

There are also data on the impact of variants of the CYP2C9 gene on the effectiveness of losartan therapy. The frequency of the GG genotype of the rs2860905 variant of the CYP2C9 gene was shown to be higher in the losartan responder group compared to the non-responder group, but these results were not statistically significant [40]. These data are consistent with the results of a study by Qayyum et al., in which a slight tendency towards the need for a higher dose of losartan was determined for carriers of the CYP2C9*3 allele by the rs1057910 variant of the CYP2C9 gene [41]. The same trend – regarding the need for a higher dose of losartan for carriers of the CYP2C9*3 allele – was determined in the study by Pedreros-Rosales et al. [42]. In view of the relatively small sample sizes in the above studies, we can assume that more significant results will be achieved by conducting repeated, larger studies.

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The results of a meta-analysis showed that CYP2D6 poor metabolizers have greater reductions in diastolic and systolic blood pressure and heart rate during metoprolol treatment and may have a higher risk of bradycardia compared to non-poor metabolizers [43]. Regarding β-blocker dosing, an association of the CYP2D6*4 variant (rs3892097) with a lower maintenance dose of metoprolol and a trend with a higher maintenance dose of carvedilol was shown for patients with heart failure [44].

Among the variants of the Cyp2C19 gene, the most common and significant variant is rs4244285 (G681A, CYP2C19*2) [45]. It was shown that among healthy individuals who received a single dose of 200 mg of labetalol orally, individuals with the AA genotype compared to GG carriers had a higher peak concentration and a higher AUC0-∞[46]. The authors also noted that this variant of the CYP2C19 gene was the only predictor of labetalol concentration, accounting for approximately 60 % of the total variance of AUC0-∞.

CYP11B2 is the key rate-limiting enzyme in the final stages of aldosterone biosynthesis. The rs1799998 (–344C>T) variant of the *CYP11B2* gene is associated with an increased risk of developing hypertension and coronary heart disease. In a study conducted in China, in patients with AH during treatment with telmisartan, a significantly greater decrease in blood pressure was noted in carriers of the C allele (carriers of the CC and CT genotypes) compared to carriers of the TT genotype [47].

The *POR* gene encodes the enzyme P450 oxidoreductase, which is an electron donor for P450 enzymes and for some other functionally active proteins and molecules. In a study by Han et al. among healthy Koreans, the maximum concentration of amlodipine in the blood was noted in carriers of the TT genotype with the g.57332T>C variant and GG with the g.56551G>A variant of the POR gene [48].

4.4 ADRB1 and ADRB2 genes

The presence of certain variants in genes encoding adrenergic receptors has functional and physiological consequences. β1-adrenergic receptors are important in the regulation of heart rate and myocardial contractility. Similarly, β2-adrenergic receptors play an important role in cardiac function, metabolism, and vascular tone.

The results of the analysis by Shahin et al. provided evidence to support the hypothesis that rs1042714 and rs1042713 in the *ADRB2* gene are important predictors of heart rate response to cardioselective β-blockade in cohorts of patients with AH [49]. In addition, Castaño-Amores et al. found that the presence of the G allele at the rs1042714 (Glu27Gln) variant of the ADRB2 gene provides a protective effect against hypotension caused by beta-blockers [50]. The GG genotype of the rs1042713 (Gly16Arg) variant of the *ADRB2* gene could also prevent hypotensive events, suggesting that the above variants in the ADRB2 gene could potentially influence the response and tolerance to beta-blockers in patients with acute coronary syndrome (ACS).

In a study by Chen et al. the rs1801253 (1165G>C, Gly389Arg) variant of the *ADRB1* gene was found to have a greater effect on the antihypertensive effect of metoprolol than variants of the *CYP2D6* gene, and the best BP reduction was observed in carriers of the GG genotype [51]. In another study, it was determined that the Gly389Arg variant of the *ADRB1* gene affects the cardioprotective effect of metoprolol in patients with myocardial infarction [52]. A study by Guerra et al. showed that the presence of alleles 27Glu of the *ADRB2* gene and 389Arg of the *ADRB1* gene in patients with heart failure may contribute to better survival when using higher doses of β-blockers [53].

In a study by Parikh et al., increased heart failure with reduced ejection fraction efficiency during BB bucindolol administration in *ADRB1* Arg389Arg carriers compared to 389Gly carriers occurred when high doses of this drug were used [54]. Other BBs administered to patients at low doses had reduced efficacy in patients with the Arg389Arg genotype compared to 389Gly carriers, suggesting a greater treatment effect at high doses.

ADRB1 rs1801253 variant is the most studied genetic polymorphism affecting response to bisoprolol. A systematic review evaluated the effect of many genetic polymorphisms on patients' response to bisoprolol, and *ADRB1* rs1801253 variant was the most relevant genetic variant in this regard [55]. Carriers of Arg389Arg with ACS in the study of Fayed et al, when treated with bisoprolol, showed a greater decrease in SBP and DBP compared to carriers of Gly389, that is, this variant is a promising predictor of response to bisoprolol [56].

4.5 *ACE gene*

The *ACE* gene, responsible for coding ACE, catalyzes the conversion of angiotensin I to angiotensin II. Consecutive effects of angiotensin II include increased blood pressure due to increased aldosterone synthesis, increased sodium and water reabsorption, increased blood volume, increased total peripheral resistance, and increased cardiac output [57].

The *ACE* gene has a diverse range of variants that affect the activity of ACE, thereby causing blood pressure fluctuations in individuals. Among these polymorphisms, I/D (or 287bp I/D, rs4646994) is the most studied variant affecting BP regulation. Individuals with genotypes II, ID, and DD may exhibit different plasma ACE concentrations, potentially contributing to variations in BP and response to ACE inhibitor therapy. The results of Hristova et al [58] suggest the effect of the I/D variant of the *ACE* gene on the level of ACE2 (ACE homologue) and chymase. On the other hand, elevated levels of ACE2 and chymase were noted in patients with uncontrolled AH. Therefore, insufficient blood pressure control with ACE inhibitor therapy may be associated with the I/D variant of the *ACE* gene. A review by Handani et al. [57] demonstrated that the D allele is associated with an increased risk of essential hypertension and an impaired response to ACE inhibitors compared with carriers of the I allele. Hypertensive patients who are carriers of the D allele may require higher doses of ACE inhibitors or alternative antihypertensive drugs for achievement of therapeutic goals. This is confirmed by a Chinese study in which no association was found between the I/D variant of the *ACE* gene and BP reduction after telmisartan treatment [46]. Early detection of this variant

contributes to the prevention of hypertension and facilitates the selection of appropriate therapy. In a study by Mu et al. [59] found a significant association between carriers of the I/D variant of the *ACE* gene and enalapril-induced cough, showing racial and age differences.

In a study by Masilela et al. among South African adults, it was determined that the rs4291 variant of the ACE gene was associated with uncontrolled hypertension during amlodipine treatment in this cohort [60].

4.6 Other candidate genes

Regarding CCB, in the study of Soria-Chacarteguiet al. [61] in volunteers who took amlodipine and had the GA genotype according to the rs34059508 variant of the *SLC22A1* gene, a significantly larger AUC_{0-72} area adjusted for dose/weight was noted. Also, in these people, a significantly higher frequency of side effects when taking amlodipine, such as dizziness and chest pain, was noted. It will be recalled that the organic cation transporter encoded by the *SLC22A1* gene is one of the main hepatic transporters that moves various drugs from the blood to hepatocytes. In the same study, it was determined that ultra-rapid metabolizers by the *CYP2D6* gene had a lower AUC_{0-72} area adjusted for the dose/weight of the given drug compared to normal, intermediate, and slow metabolizers. Also, participants with higher *CYP2D6* gene activity showed lower exposure to amlodipine and needed less time to clear it from the blood.

The efficacy of another CCB, felodipine, in the study by Yuan et al [62] had individual differences, especially under the influence of the *CACNA1C* rs1051375 variant, for which a significant association between SBP reduction was observed, and the *ABCB1* rs1045642, which was correlated with SBP reduction in healthy Chinese people with repeated use of this drug. As is known, the ABCB1 gene encodes the cellular transmembrane transporter P-glycoprotein, which removes a wide range of xenobiotic, including medicinal, compounds from cells.

As for β-blockers, the clearance of bisoprolol in the study by Fontana et al. was associated with rs11029955, which is located near the *CCDC34* gene on chromosome 11. CCDC34 is a member of the coiled-coil domain, which is expressed in several human tissues and is associated with the development of various types of oncology, and may play a role in cell proliferation and anti-apoptosis This variant is in linkage disequilibrium with 4 other intronic variants of the *CCDC34* gene – rs7935021, rs61887779, rs1871254 and rs2291022 – which are not currently associated with any disease or trait. Each copy of the minor allele of rs11029955 was associated with a 2.2 L/h increase in bisoprolol clearance. In an independent cohort of patients with hypertension, the rs11029955 variant was also associated with a decrease in heart rate during a 4-week treatment with bisoprolol [63].

Regarding ARBs and ACE inhibitors, losartan can lower serum urate levels by inhibiting the activity and mRNA expression of the urate transporter enzyme URAT1, but the magnitude of the effect of this drug on urate levels varies among patients, suggesting that differences in the URAT1 transporter may potentially be associated with the uricosuric activity of losartan. In the study by Wu et al, the *URAT1* rs3825016 variant influenced the uricosuric effect of losartan [64]. In particular, it was shown that carriers of the heterozygous CT genotype had a more significant decrease in serum urate levels compared to carriers of the CC genotype.

Another research group, Shin et al, demonstrated that diplotypes for variants rs2032582 (2677G>T) and rs1045642 (3435C>T) of the *ABCB1* gene can significantly increase the absorption of losartan in the early phase, but do not affect the overall absorption of the drug [65].

A group of researchers led by C. Masilela established an interaction between *VEGFA* (rs699947), *ABO* (rs495828) and *NOS3* (rs2070744) gene variants with a better response to enalapril in South African adult patients with AH [66]. VEGF is an important angiogenic growth factor encoded by the *VEGFA* gene. Haplotype analysis of *VEGFA* gene variants rs699947, rs1570360, and rs2010963 demonstrated that AGG haplotype carriers had a better BP reduction after enalapril treatment, while CGG haplotype carriers had the opposite effect [67].

After administration, enalapril is hydrolyzed to the active diacid metabolite enalaprilat. This bioactivation is catalyzed mainly by carboxylesterase 1 (CES1). Her et al. demonstrated that the rs71647871 (G143E) loss-of-function variant of *CES1* significantly impaired the activation of enalapril and its systolic BP-lowering effect in healthy volunteers [68].

Regarding side effects, in hypertensive patients, genome-wide sequencing determined that genes variants *PNPT1* rs13015243, *PNPT1* rs13009649, and *PCGF3* rs1044147 were significantly associated with enalapril-induced cough [69]. *PNPT1*, which is expressed in brain and spinal cord tissues, as well as lungs, encodes polyribonucleotide nucleotidyltransferase 1. This enzyme is mainly localized in the intermembrane space of mitochondria, participates in RNA degradation, processing, and polyadenylation and mediates RNA import into mitochondria. Its overexpression increases the synthesis of reactive oxygen species in mitochondria, which causes the development of oxidative stress, which activates nociceptive sensory nerve endings that innervate the respiratory tract and can induce the cough reflex. The *PCGF3* gene encodes a protein of the same name, which is expressed mainly in the brain. Its functions are poorly understood, but there is an assumption that it can take part in the differentiation of neurons.

According to the results of the study by Ghafil et al [70], carriers of AA and AT genotypes of *AT1R* rs275651 variant, are more prone to surgery after an attack of ACS, it is recommended to adjust the appropriate therapeutic dose of the ACE inhibitor captopril, as they may require higher doses of the drug. The AT1R gene encodes the angiotensin II type 1 receptor (AT1 receptor), which is part of the renin-angiotensin system that regulates blood pressure and the balance of fluids and salts in the body. This system produces angiotensin II, which binds to the AT1 receptor and stimulates constriction of blood vessels, resulting in an increase in blood pressure.

Flaten et al. found in a pilot study that variants of *AGT*, *REN* and *ACE2* genes are associated with successful

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lisinopril treatment of patients with uncontrolled hypertension, but the study was conducted with a rather small number of participants and its results need further confirmation [71].

With regard to diuretics, a large-scale study identifying variants associated with chlorthalidone efficacy in African Americans identified eight variants statistically associated with BP change [72]. The most significant association in the current study was determined for the intronic variant rs191702725 of the *CDHR2* gene.

According to Singh et al [73] gene variants of *WDR92* and *PPP3R1* are novel candidates that may help explain the genetic basis of BP response to thiazide and thiazide-like diuretics and help identify patients who are better suited to the above drugs compared to β-blockers for BP control.

A GWAS-study was conducted in Europeans to investigate the effect of thiazide diuretic use on plasma low-density lipoprotein, high-density lipoprotein, and triglyceride concentrations, in which the rs2199576 variant was identified near the *PVRL2* locus, a gene located within 100 kb of *TOMM40* and of the *APO* cluster, which are associated with the concentration of lipids in the blood [74]. These data may help further study the pathways that influence the adverse effects of thiazide diuretics.

Therefore, due to the numerous studies in the field of pharmacogenetics of antihypertensive drugs and their sometimes contradictory results, the data presented are limited to only a few options that can really influence the metabolism of drugs used to normalize blood pressure and are presented in Table 1.

Table 1

List of pharmacogenetic markers that affect antihypertensive drugs

Gene	Variant	Name and class of the drug	Influence of the variant	Link
NOS3	rs1799983	Amlodipine; CCB	For carriers of the variant, the advantage of using amlodipine compared to lisinopril has been demonstrated	[29]
	rs2070744	ARBs and ACE inhibitors (enalapril and olmesartan)	carriers of the C allele have a better response to these medications. In general, the TC genotype is more common in those who respond well to treatment with these drugs	[1, 2]
ACE	I/D	ACE inhibitors and ARBs	carriers of the D allele may need higher doses of these drugs or alternative medications	[47]
TRIB3	rs2295490	CCB (azelnidipine and nitrendipine); ARBs	Carriers of the AA genotype had a better antihypertensive effect after CCB treatment. Carriers of AG and GG genotypes benefited from ARBs antihypertensive therapy with a greater change in BP	[31]
	rs6037475	CCB (felodipine)	Patients with the CC genotype had significantly higher BP and SBP than carriers of the TT genotype	[32]
ADRB2	rs1042714 rs1042713	β-blockers	The presence of the G allele (rs1042714) and the GG genotype (rs1042713) provides a protective effect against hypotension caused by taking drugs of this class. Carriers of these variants with heart failure had better survival when using higher doses of drugs of this class	[50], [53]
ADRB1	rs1801253	β-blockers (metoprolol, bucindolol, bisoprolol)	The best blood pressure reduction was observed in carriers of the Gly389Gly genotype. In carriers with heart failure, better survival was observed with higher doses of drugs of this class. Exacerbation of heart failure with reduced ejection fraction efficiency during bucindolol in Arg389Arg carriers occurs at a high dose. Other β-blockers used at low doses had reduced efficacy in patients with the Arg389Arg genotype. Carriers of Arg389Arg with GCS when treated with bisoprolol showed a greater decrease in SBP and DBP.	[49], [51], [53], [54]
CYP3A5	rs776746 rs15524 rs4646453	CCB (amlodipine)	Carriers of CC genotypes for rs776746 and AA for rs15524 have an increased risk of peripheral edema, while patients who are carriers of AC and AA genotypes for rs4646453 have a reduced risk of peripheral edema	[34]
		ARB (tileridipine)	Carriers of the CC genotype with the rs776746 variant had a longer half-life than wild-type carriers	[35]

5. Genes of proven influence on the development of hypertension in women of reproductive age, pregnant women, women in childbirth and their response to treatment during pregnancy

To date, hypertension in pregnancy is still defined as SBP ≥ 140 mmHg and DBP≥ 90 mmHg. Women with chronic hypertension have a higher incidence of pre-eclampsia, the need for cesarean section, preterm delivery, critically low birth weight, and possible perinatal death. Such women also have a higher risk of developing cardiovascular disease in the future [75, 76].

When treating pregnant women with hypertension, the efficacy of the antihypertensive agent must be balanced against the risk to the fetus. Initial antihypertensive therapy

should include an acceptable first-line agent [77]. All of the most commonly used and recommended antihypertensive drugs belong to different classes and cross the placenta, including drugs such as labetalol, nefidipine, methyldopa and metaprolol. In a randomized controlled trial, the use of nifedipine monotherapy led to a higher frequency of achieving the target outcome than the use of labetalol or methyldopa, but all three drugs were effective initial treatment options for severe hypertension [78].

Nifedipine is a CCB that causes vasodilation and decreases systemic vascular resistance. High doses of this drug may cause reflex tachycardia, headache, and peripheral edema. The enzyme CYP3A4 plays an important role in the metabolism of nifedipine. According to Khatriue et al., pregnancy-related hormones such as estradiol, estriol, esterol, progesterone, and cortisol, alone or in combination, enhance the metabolism of nifedipine in human hepatocytes by inducing the expression of this enzyme and altering the expression of other key CYP proteins in an isoform-specific manner [79]. Abduljalil et al. demonstrated that CYP3A4 activity increased 1.25, 1.75, and 2.32-fold in pregnant women compared to nonpregnant women at the end of the first, second, and third trimesters, respectively [80].

Labetalol is a combined β-blocker whose general effect is vasodilation without reflex tachycardia or decreased cardiac output. Glucuronidation of labetalol is the major elimination pathway and is catalyzed by glucuronosyltransferases (UGT). Khatri R et al. recently demonstrated that exposure to the above hormones also significantly enhanced labetalol metabolism in hepatocytes by inducing UGT1A1 protein levels [81], which correlates with the results of Jeong et al.

In general, it can be argued that higher doses of labetalol and nifedipine may be required during pregnancy to maintain the desired concentrations of these drugs and achieve the required therapeutic effect.

Methyldopa is an alpha-2 adrenergic receptor agonist that inhibits vasoconstriction by reducing the release of catecholamines. This drug does not bind to plasma proteins and its bioavailability after oral administration is 25-50 % [83]. Approximately 50 % of the dose is excreted unchanged in the urine, and the remainder is metabolized by sulfation and O-methylation by sulfotransferases and catechol-O-methyltransferase, respectively. At present, there are no data on the pharmacokinetics of methyldopa in pregnancy, although it is believed that changes in the pharmacokinetics of this drug associated with pregnancy are either absent or not clinically significant.

Metoprolol is a widely used antihypertensive drug that is primarily metabolized by CYP2D6. Because clearance of the drug increases during pregnancy, metoprolol is eliminated more rapidly, putting women at risk for increased blood pressure. This reduction in efficacy may be particularly pronounced in patients who are very fast metabolizers of CYP2D6. Women with low CYP2D6 metabolism have higher plasma concentrations of this drug, which may be associated with reduced cardioselectivity and a potentially higher incidence of adverse effects [84].

Conclusions

Inconsistencies in study results may be explained by inter-ethnic differences in the distribution of variants analyzed, epigenomic changes that may mask the contribution of variants, or the approach to data analysis used.

The studies included in this review used two main approaches: candidate gene analysis and genome-wide association analysis. The polygenic nature of hypertension greatly complicates the search for clinically relevant variants and relationships between individual genes and response to drugs used to treat hypertension in different ethnic groups.

Drug response is associated with multifactorial and polygenic complex traits, and the above approaches may miss some associations that can only be identified by examining combinations of multiple genomic regions. Overall, studies have shown that genotype-optimized antihypertensive therapy is more effective in avoiding serious adverse events in patients and achieving better clinical outcomes and survival. Genotyping of patients with adverse drug reactions can help to design new drug therapy regimens and thus improve their treatment outcomes. The creation of a pharmacogenomic strategy to select the most effective and well tolerated drug treatment regimen for hypertension is extremely important, as it will lead to a lower number of drugs required per patient and better blood pressure control, which in the long run will help avoid cardiovascular and renal complications in patients, as well as improve their quality of life and life expectancy. Therefore, studies on the pharmacogenetics of drugs that help control hypertension require further efforts by scientists to discover new genes and variants and to consider the epigenetic and regulatory pathways of their action.

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ФАРМАКОГЕНОМНА СТРАТЕГІЯ ПІДБОРУ ГІПОТЕНЗИВНИХ ПРЕПАРАТІВ ТА ПЕРСПЕКТИВИ ЇЇ ВИКОРИСТАННЯ У ВАГІТНИХ ЖІНОК

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Резюме.

Серцево-судинні захворювання є однією з основних причин смерті в усьому світі і артеріальна гіпертензія (АГ) належить до найсильніших факторів ризику їх розвитку. Проблема АГ є також актуальною під час вагітності, оскільки підвищений артеріальний тиск може бути небезпечним як для матері, так і для плода, викликаючи прееклампсію та передчасні пологи. За останніми даними, кількість хворих на АГ зростатиме. Через полігенну та мультифакторну природу терапевтичної відповіді на препарати необхідні подальші дослідження в цій галузі з метою написання доказових рекомендацій для клініцистів, які допоможуть оптимізувати антигіпертензивну терапію.

Метою даного огляду було узагальнити інформацію з наукових публікацій, мета-аналізів, настанов за 2018-2023 роки щодо варіантів в генах, які впливають на метаболізм різних класів медикаментів, які застосовуються при лікуванні АГ, в тому числі, під час вагітності та пов'язані з розвитком АГ.

Основу патогенезу АГ складають як зниження вазодилатації, так і збільшення об'єму циркулюючої крові. Артеріальна жорсткість призводить до зменшення вазодилатації, а водно-натрієва затримка викликає збільшення об'єму крові. Додаткові фактори, такі як ренін-ангіотензин-альдостеронова система, симпатична нервова система та варіанти генів, впливають як на розширення судин, так і на об'єм крові. Крім того, існують складні взаємодії між цими факторами. Як вроджений фактор, варіанти генів можуть одночасно впливати на всі вищезазначені аспекти.

Настанови Американської кардіологічної асоціації (АНА) та Європейського товариства кардіологів (ESC) рекомендують використовувати препарати з наступних 5 класів: діуретики, блокатори кальцієвих каналів (БКК), ***блокатори*** β-адренорецепторів (β-блокатори), інгібітори ангіотензинперетворювального ферменту та блокатори рецепторів до ангіотензину II.

У дослідженнях, які включені в даний огляд, використовувалися два основні підходи: аналіз гена-кандидата і аналіз повногеномної асоціації. Полігенна природа АГ значно ускладнює пошук клінічно значущих варіантів, а також взаємозв'язків між окремими генами та реакцією на медикаменти, які використовуються для керування АГ у представників різних етнічних груп.

Серед генів-кандидатів, що можуть впливати на ризик виникнення АГ – гени потенціал-залежних кальцієвих каналів (CACNA1A, CACNA1C, CACNA1S і CACNB2), NEDD4L, ADD1, miR. Ряд генетичних поліморфізмів пов'язані як із впливом на розвиток артеріальної гіпертензії, так і реакцією на лікування – eNOS, TRIB3, CYP, POR, ADRB1, ADRB2, ACE. При лікуванні вагітних жінок з АГ ефективність антигіпертензивного засобу повинна бути збалансована з ризиком для плода. Початкова антигіпертензивна терапія має включати один прийнятний препарат першого ряду.

Створення фармакогеномної стратегії для підбору найбільш ефективного і добре переносимого режиму медикаментозного лікування АГ надзвичайно важливе, оскільки це призведе до меншої необхідної кількості препаратів на пацієнта та кращого контролю артеріального тиску, допоможе уникнути серцево-судинних і ниркових ускладнень, покращить якість та тривалість життя.

Ключові слова: артеріальна гіпертензія; гени ризику артеріальної гіпертензії; фармакогенетика гіпотензивних препаратів; вагітні жінки.

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