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The Pharmacology of Antihypertensive Drugs: Genetic Variability and Drug Responses

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Abstract

Hypertension is a significant global health challenge, affecting over 1.5 billion individuals worldwide and contributing substantially to cardiovascular disease morbidity and mortality. Despite the availability of various antihypertensive drugs, inter-individual variability in drug responses remains a persistent issue, leading to suboptimal blood pressure control and increased risk of adverse outcomes. Genetic polymorphisms have been identified as key factors influencing the pharmacological efficacy of antihypertensive agents, including calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, ß-blockers, and diuretics. Single nucleotide polymorphisms (SNPs) in genes encoding drug targets, metabolizing enzymes, and transporters modulate drug responses through diverse mechanisms, such as altering receptor sensitivity, ion transport, and metabolic pathways. Genome-wide association studies have revealed numerous loci associated with blood pressure responses to specific antihypertensive drugs, highlighting the complex genetic architecture underlying hypertension and its treatment. Notably, ethnic variations in drug responses underscore the need for personalized approaches to hypertension management, as exemplified by the differential efficacy of diuretics and calcium channel blockers in Black populations compared to White populations. While these findings provide valuable insights, further research is necessary to refine clinical guidelines and facilitate the integration of pharmacogenomics into routine practice. Addressing the complexities of genetic variability in antihypertensive drug responses will pave the way for optimized and individualized therapeutic strategies, ultimately reducing the prevalence of uncontrolled hypertension and its associated complications.

Keywords: Antihypertensive Drugs, Hypertension, Genetic Variability, Drug Response, Pharmacology, Diuretics.

Introduction

Hypertension is recognized as one of the most significant modifiable risk factors for cardiovascular diseases, with its prevalence steadily rising globally (Oliveira-Paula et al., 2019). Current estimates indicate that

more than 116.4 million individuals are affected by this condition, which is associated with 2,303 deaths related to cardiovascular disease (CVD) daily. Projections suggest that within the next 20 years, the prevalence of hypertension will increase by 60%, reaching a total of over 1.5 billion individuals worldwide. In the United States, approximately 46% of adults are estimated to have hypertension, among whom only 80% are aware of their condition, and an even smaller proportion adheres to pharmacological treatment regimens. Among those who are treated, adequate blood pressure control is achieved in roughly 53% of individuals (Yoon et al., 2012, pp. 2009–2010).

The high prevalence of undiagnosed and uncontrolled hypertension can be attributed to the frequent absence of specific clinical manifestations, earning hypertension the label of a "silent killer." Additionally, poor treatment efficacy and low adherence to therapy, often due to adverse reactions to active drug ingredients, persist despite growing public awareness of hypertension and its complications. Variability in the efficacy of certain therapies may be partially explained by inter-individual genetic differences. Genetic studies within families suggest that heritability accounts for 30% to 50% of the inter-individual variability in blood pressure (BP) levels. Genome-wide studies have further confirmed that genetic factors not only contribute to blood pressure elevation but also influence individual responses to antihypertensive therapies. Given the polygenic nature of hypertension, no single genetic locus can serve as a universal clinical target; therefore, understanding complex traits, such as drug response phenotypes, requires the evaluation of interactions among multiple loci. Genetic variability may influence drug response through mechanisms such as the modulation of genes involved in hypertension pathophysiology, alterations in mechanistic drug–gene interactions, and polymorphisms in genes encoding drug transporters. Additionally, genetic polymorphisms in drug-metabolizing enzyme genes and pleiotropic genes involved in metabolic pathways and cascades can impact therapeutic responses. Genome-wide association studies (GWASs) have identified variants associated with drug efficacy and adverse drug reactions. However, given the multigenic and multifactorial nature of drug response phenotypes, further research is needed to develop reliable clinical guidelines (Zanger, 2010). The most common polymorphisms in genes influencing drug response are summarized below.

2. Calcium Channel Blocking Agents

2.1 Mechanism of Calcium Channel Blocker Action

Calcium channel blockers (CCBs) are pharmacological agents that bind to and inhibit predominantly L-type calcium channels located on cardiac and vascular smooth muscle cells (SMCs). These blockers reduce the influx of calcium ions into vascular smooth muscles, promoting muscle relaxation and vasodilation. This results in decreased vascular resistance and, consequently, a reduction in arterial blood pressure. The different subclasses of calcium channel blockers act at distinct locations. For instance, dihydropyridines, such as amlodipine and nifedipine, are selective for vascular tissues, verapamil targets cardiac tissues, and diltiazem exerts effects on both the heart and blood vessels (Laurent, 2017).

2.2 Polymorphisms in Genes Affecting CCB Response

Numerous studies have identified single-nucleotide polymorphisms (SNPs) in genes encoding ion channels, including the large-conductance voltage- and calcium-sensitive potassium channel β1 (KCNMB1), voltage-gated calcium channels α1C (CACNA1C), α1D (CACNA1D), β2 (CACNB2), and the ERG potassium channel (KCNH2). These genetic variants have been shown to modify antihypertensive responses to calcium channel blockers and influence the risk of adverse cardiovascular outcomes (He et al., 2013). Furthermore, variations in genes encoding members of the HECT domain E3 ubiquitin ligase family (NEDD4L) and the ATP-binding cassette subfamily B member 1 (ABCB1) have been implicated in blood pressure regulation in response to antihypertensive medications.

The INVEST-GENES study demonstrated that the KCNMB1 genotype could influence verapamil SR responses in White, Hispanic, and Black hypertensive patients with cardiovascular disease (CAD). The KCNMB1 gene encodes the β1 subunit of the large-conductance potassium channel (BK or Maxi-K type). Reduced functionality of this protein has been associated with decreased calcium sensitivity, elevated blood pressure, and cardiac hypertrophy. Two nonsynonymous polymorphisms in the KCNMB1 gene, Glu65Lys (rs11739136) and Val110Leu (rs2301149), were identified as modulators of inter-patient variability in blood pressure response to verapamil. Carriers of the Lys65 variant achieved blood pressure targets faster (1.47 [interquartile range (IQR 2.77)] months) compared to Glu65 homozygotes (2.83 [IQR 4.17] months; $p = 0.01$). Additionally, the Leu110 allele reduced the risk of nonfatal myocardial infarction in patients treated with verapamil but not in those treated with atenolol.

Candidate association studies have revealed genetic variants in calcium channels that could facilitate the selection of calcium channel blockers or β-blockers. For example, the CACNA1C gene, encoding the alpha1c-subunit of the L-type calcium channel, has been implicated in such variability (Eadon et al., 2018). Beitelshees et al. investigated eight SNPs within CACNA1C to examine associations between verapamil and atenolol treatment efficacy and the occurrence of primary outcomes such as stroke, myocardial infarction, and death. Among individuals with the AA genotype, verapamil treatment was associated with a reduced rate of primary outcomes (OR 0.54, 95% CI 0.32–0.92), while GG genotype carriers exhibited a higher risk of a

composite primary outcome (OR 4.59, 95% CI 1.67–12.67). Similarly, Bremer et al. studied the efficacy of various calcium channel blockers, including amlodipine, in Caucasian individuals with hypertension. They identified three variations in CACNA1C significantly associated with responses to amlodipine and felodipine, with two variations, rs22368032 and rs2239050, correlating with uncontrolled hypertension. However, these findings require validation through larger studies involving more diverse populations due to the small and homogeneous sample size in the initial research.

Variants in the CACNB2 gene, encoding the regulatory β2 subunit of the voltage-gated calcium channel, have also been associated with cardiovascular outcomes in individuals randomized to verapamil treatment. Carriers of the GG genotype of SNP rs2357928 within a promoter region showed an increased risk of primary outcomes when treated with verapamil compared to atenolol. In a Japanese retrospective study, three SNPs were identified: rs527974 in CACNA1C and rs312481 and rs3774426 in CACNA1D, which influenced sensitivity to amlodipine and other calcium channel blockers in individuals with uncontrolled hypertension (Kamide et al., 2013). The combined presence of rs312481G/A and rs3774426C/T in CACNA1D was linked to significant blood pressure reductions, with CC genotype carriers demonstrating better responses, as evidenced by lower systolic blood pressure.

Polymorphisms in genes responsible for drug metabolism also influence drug responses. For example, a splicing defect associated with the 14690G>A polymorphism in exon 7 of the CYP3A5 gene (CYP3A5*6, rs10264272) results in exon 7 deletion and reduced enzyme activity, which in turn affects antihypertensive drug responses. Langaee et al. utilized a haplotype approach to investigate CYP3A5 mutations' effects on blood pressure responses to verapamil in Black, Hispanic, and White populations. Their findings indicated that blood pressure responses to verapamil were somewhat influenced by the number of functional CYP3A5 alleles in Black and Hispanic populations, with carriers of two functional alleles exhibiting the poorest responses.

The activity of cytochrome P450 3A4/5 (CYP3A4/5) enzymes is particularly significant for the metabolism of amlodipine, a first-line long-acting calcium channel blocker that improves blood flow by inhibiting calcium influx via L-type calcium channels in vascular smooth muscle cells [16,30]. Polymorphisms in genes involved in amlodipine metabolism, such as CYP3A4*1B (-392A/G, rs2740574), have been identified as prognostic markers for blood pressure responses. For instance, in African American women with early hypertensive nephrosclerosis, carriers of the A allele were more than three times as likely to achieve a target mean arterial pressure (MAP) of 107 mm Hg ($p = 0.02$). Gender differences in P-glycoprotein (PgP) levels, which are two to three times higher in men than in women, have been implicated in the intracellular concentrations of amlodipine and subsequent response variability. Additionally, enhanced hepatic clearance of CYP3A and PgP in women may be attributed to physiological differences such as body weight, organ size, fat composition, and glomerular filtration rate. Polymorphisms in CYP3A4 (T16090C, rs2246709) have also been associated with blood pressure responses to amlodipine in individuals randomized to lower MAP groups (≤92 mm Hg). Irrespective of gender, carriers of the 16090C allele were twice as likely to achieve the target MAP of 107 mm Hg compared to T allele carriers ($p = 0.01$), with this effect appearing specific to amlodipine rather than ramipril (Bhatnagar et al., 2010).

In their study, Kim et al. investigated the influence of the CYP3A53 (A6986G, rs776746) genotype on the pharmacokinetics and pharmacodynamics of amlodipine in a cohort of healthy Korean males. The CYP3A51 allele is functional, whereas the CYP3A53 variant, due to a mutation in intron 3, leads to a splicing defect and the production of non-functional proteins. The results revealed a statistically significant 20% difference in the oral clearance of amlodipine between CYP3A51 carriers (27.0 ± 8.2 L/h) and CYP3A53/3 carriers (32.4 ± 10.2 L/h) ($p = 0.063$). Additionally, CYP3A51 carriers exhibited a significantly higher peak plasma concentration (3.8 ± 1.1 ng/mL) compared to CYP3A53/*3 carriers (3.1 ± 0.8 ng/mL) ($p = 0.037$). Despite these differences, no significant variations in blood pressure (BP) or pulse rate were observed between the groups. The authors suggested that polymorphisms in the CYP3A5 gene might influence the inter-individual variability in amlodipine disposition. However, Zhu et al. argued that CYP3A4 is primarily responsible for amlodipine dehydrogenation, implying that CYP3A5 polymorphisms are unlikely to impact its pharmacokinetic variability.

Amlodipine's bioavailability and concentration may also be affected by polymorphisms in the ATP-binding cassette subfamily B member 1 (ABCB1) gene, also known as multi-drug resistance 1 (MDR1) [16]. The ABCB1 gene encodes P-glycoprotein (P-gp), a drug efflux pump that regulates amlodipine accumulation in cells. Polymorphisms in exon 26 (C3435T, rs1045642) of the ABCB1 gene have been shown to reduce P-gp expression and activity, thus influencing the absorption and tissue concentration of substrates like amlodipine. Zuo et al. demonstrated that the C3435T polymorphism in the ABCB1 gene affects amlodipine plasma concentrations in hypertensive Han Chinese patients without altering treatment efficacy. Carriers of the 3435TT genotype exhibited lower P-gp expression and a 1.5-fold higher oral clearance (CL/F) of amlodipine compared to 3435CC and 3435CT carriers (Zuo et al., 2014).

3. Angiotensin-II Receptor Blockers (ARB) and Angiotensin-Converting Enzyme Inhibitors (ACEi)

The renin-angiotensin-aldosterone (RAA) system is critical for modulating blood pressure and sodium balance through mechanisms involving the kidney, cardiovascular system, and central nervous system. Angiotensin II (Ang II), the system's final effector, exerts its effects by binding to angiotensin II type 1 receptors (AT1R) in various tissues, leading to vasoconstriction, sodium reabsorption, and enhanced sympathetic activity. Drugs targeting this system include angiotensin-converting enzyme inhibitors (ACEi), which block Ang II formation, and angiotensin II receptor blockers (ARB), which antagonize Ang II by binding to AT1R.

Polymorphisms in Genes Affecting the ARB and ACEi Response

Polymorphisms in genes within the RAA system can influence the pharmacogenomic response to ARBs and ACEi. The efficacy of ARBs has been linked to pleiotropic effects, including nitric oxide (NO) production by endothelial NO synthase (NOS3) [38,39]. Mason et al. found that endothelial cells homozygous for the C allele in the −786T/C polymorphism of NOS3 (rs2070744) respond to olmesartan with increased NO production, suggesting that hypertensive carriers of the C allele might show enhanced responses to olmesartan and enalapril. Similarly, Oliveira-Paula et al. reported that the T allele for the NOS3 −665C/T SNP (rs3918226) correlates with better responses to enalapril, whereas the A allele of the NOS3 tagSNP (rs3918188) and the CAG haplotype were associated with reduced responses.

Genome-wide association studies (GWAS) have identified multiple loci associated with BP responses to ARBs. For example, rs4953035 near the LRPPRC region correlates with systolic BP responses to losartan and candesartan. Another GWAS revealed that hypertensive carriers of the GG genotype for rs10752271 in the CAMK1D gene, involved in aldosterone synthesis, respond more favorably to losartan. Other SNPs, such as rs11020821 near the FUT4 gene, rs11649420 in the SCNN1G gene, and rs3758785 in the GPR83 gene, were linked to candesartan response. The GG genotype for rs11649420 in SCNN1G showed a three-fold greater BP response to candesartan compared to AA+AG genotypes, an effect possibly moderated by sodium reabsorption counter-regulation (Turner et al., 2012).

Polymorphisms in CYP11B2, encoding aldosterone synthase, also affect responses to ARBs. For instance, the −344C/T SNP (rs179998) was linked to variable BP responses, with some studies associating the C allele and others the T allele with better outcomes. The GENRES study identified the rs3814995 variant in NPHS1, encoding nephrin, as significantly associated with BP responses to losartan, suggesting a role for nephrin in BP regulation.

Regarding ACEi, polymorphism rs16960228 in PRKCA (protein kinase C alpha) is associated with variable BP responses. Oliveira-Paula et al. [50] found that the GG genotype correlates with improved BP responses to enalapril, while GA+AA genotypes were associated with diminished responses. Additionally, Silva et al. observed that the TC/CC genotypes of the NOS3 −786T/C SNP and the TT genotype of the BDKRB2 −58C/T SNP are more prevalent in good responders to enalapril. Combined analyses of PRKCA, NOS3, and BDKRB2 polymorphisms highlighted gene–gene interactions influencing ACEi responses, particularly in enhancing NO production and vasodilation through PKCα-mediated NOS3 upregulation (Oliveira-Paula et al., 2017). These findings suggest that responses to ACEi and ARBs are shaped by complex genetic interactions.

4. β-Adrenergic Antagonists (β-Blockers)

4.1. Effects of β-Adrenergic Blocker Actions

Although β-blockers are not considered first-line antihypertensive agents according to the guidelines of the Joint National Committee (JNC8) on hypertension management they remain extensively utilized in specific patient populations. Beyond their antihypertensive effects, which involve the inhibition of targets on juxtaglomerular cells of the kidney, the suppression of renin secretion, and the subsequent reduction in circulating angiotensin II, β-blockers also decrease myocardial contractility, heart rate, and cardiac output. Research has shown that β-blockers positively influence endothelial dysfunction and are implicated in endothelial and vascular mechanisms that contribute to blood pressure (BP) reduction (Li et al., 2011).

4.2. Polymorphisms in Genes Affecting the Adrenergic Receptor Blocker Response

The principal protein target of all β-blockers is the β1-adrenergic receptor encoded by the ADRB1 gene. Multiple studies have investigated polymorphisms within the ADRB1 gene that could alter the receptor's function or modulate its drug response. Two polymorphisms, rs1801252 (Ser49Gly) and rs1801253 (Arg389Gly), have been shown to influence intracellular signaling mediated by the β1-adrenergic receptor. The Ser49 and Arg389 alleles enhance intracellular responses to β1-adrenergic receptor agonists compared to the alternative alleles. Observations of varying β-blocker responses among Black and Caucasian populations spurred genome-wide association studies (GWAS) to identify ethnicity-related polymorphisms. The INVEST-GENES study, encompassing an ethnically diverse and elderly cohort of hypertensive patients with coronary artery disease (CAD), identified the ADRB1 Ser49-Arg389 haplotype as significantly associated with an increased risk of all-cause mortality (odds ratio 3.66, 95% CI 1.68–7.99), irrespective of whether one or two alleles were present. The mortality risk was pronounced in individuals treated with verapamil but diminished in those receiving atenolol. Accordingly, the authors suggested that individuals with this haplotype might benefit more from β-blocker therapy due to a lower mortality risk. Conversely, findings from the Secondary Prevention

of Small Subcortical Strokes (SPS3) trial revealed that atenolol-treated carriers of the Gly49 allele (ADRB1) experienced a heightened risk of major adverse cardiovascular events (hazard ratio, HR 2.03; 95% CI 1.20–3.45), prompting a recommendation for calcium channel blocker (CCB) therapy for these patients.

Further, Johnson et al. reported enhanced BP responses to metoprolol among White, African American, and Hispanic carriers of the Arg/Arg genotype (Arg389Gly) compared to Gly allele carriers. Similarly, among hypertensive Chinese individuals with the 389Arg/Arg genotype, treatment with carvedilol yielded superior BP reductions compared to those with the Gly allele. However, contrasting evidence was reported by Chen et al. who observed improved antihypertensive responses to metoprolol among individuals with the Gly/Gly genotype for the Arg389Gly polymorphism. European prospective studies, on the other hand, failed to identify any association between the Arg389Gly polymorphism and BP responses to β-blockers (Suonsyrjä et al., 2010).

Adrenergic signal transduction, mediated via adrenergic receptors and G protein pathways, is critical for rapid cardiovascular adaptation. Polymorphisms within G protein–coupled receptors (GPCRs) affecting drug responses have been extensively investigated. The PEAR and INVEST cohorts identified polymorphisms within the GRK4 gene that modulate atenolol-mediated BP reduction and cardiovascular outcomes. GRK4 contributes to BP regulation by phosphorylating GPCRs, potentially including β1-adrenergic receptors. The nonsynonymous single nucleotide polymorphisms (SNPs) A142V (rs1024323), R65L (rs2960306), and A486V (rs1801058) have been studied for their roles in enhancing GRK4 functionality, enabling GPCR desensitization. Vandell et al. demonstrated that GRK4 65L and 142V variants, as well as the 65L-142V haplotype, reduced BP responses to β-blocker monotherapy and increased the risk of adverse cardiovascular outcomes. These GRK4 variants were associated with attenuated BP responses to atenolol across both Caucasian and African American populations (Vandell et al., 2012).

In GWAS involving metoprolol-treated individuals in the PEAR-2 study and atenolol-treated individuals in the PEAR study, the SNP rs294610 in the FGD5 gene was associated with improved BP responses to both metoprolol and atenolol [68]. Carriers of the A allele exhibited notably better BP responses. Other studies have linked FGD5 loci to BP phenotypes. For example, a European American cohort revealed that FGD5 loci correlated with diastolic and systolic BP levels. Research also implicated FGD5 in vascular remodeling processes, endothelial cell apoptosis, and proangiogenic activities, underscoring its potential role in hypertension and vascular diseases.

Additional analyses from the PEAR-2 and PEAR studies identified the rs45545233 polymorphism in the SLC4A1 gene as significantly associated with reduced BP responses to β-blockers. This gene encodes a glycoprotein involved in ion exchange and transport in erythrocytes and kidney collecting ducts. The SLC4A1 gene has been associated with hypertension and BP variability in the Japanese population. Furthermore, Gong et al. identified deletions within SLC25A31 and LRRC15 intronic regions that were linked to enhanced BP responses to β-blockers among hypertensive African Americans.

In the Nordic Diltiazem (NORDIL) study, involving over 10,000 participants, the rs12946454 SNP in the PLCD3 gene was found to modulate BP responses to diltiazem. The T allele was associated with increased systolic and diastolic BP responses. Similarly, variations in the ACY3 gene, including rs2514036, impacted atenolol BP responses in men and bisoprolol responses in Caucasians (Rimpelä et al., 2017).

Polymorphisms also influence the pharmacokinetics of β-blockers. For example, the cytochrome enzyme CYP2D6, pivotal in β-blocker metabolism, exhibits genotypic variations that affect BP responses. Based on robust evidence, the Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association has provided dosing recommendations for metoprolol according to CYP2D6 genotypes. However, the clinical utility of CYP2D6 genotyping for guiding metoprolol therapy in hypertensive patients remains debated due to inconsistent findings from other studies.

5. Diuretics

The Mechanism of Diuretic Action

Diuretics, particularly thiazide and thiazide-like diuretics, are recommended as first-line treatments for many patients with hypertension. The thiazide diuretic hydrochlorothiazide operates by inhibiting the sodium chloride cotransporter located in the distal convoluted tubule of the nephron. Initially, these drugs exert antihypertensive effects by promoting sodium excretion (natriuresis) and reducing extracellular fluid volume, leading to a decline in cardiac output. Over the long term, their effects involve a decrease in vascular resistance, potentially through the inhibition of the sympathetic nervous system and/or the renin–angiotensin system.

Polymorphisms in Genes Affecting Diuretic Response

As the effects of diuretics are mediated through diverse mechanisms, several candidate genes have been identified that may influence individual responses to these drugs. The efficacy of hydrochlorothiazides (HCTZs) when used in monotherapy may be diminished by factors linked to inter-individual variability, potentially leading to increased mortality in patients with uncontrolled hypertension. Furthermore, thiazides may induce adverse effects, including hypokalemia, impaired glucose tolerance, elevated serum cholesterol, and increased uric acid levels. These adverse reactions are influenced by factors such as inter-individual variation,

age, gender, and ethnicity. Single nucleotide polymorphisms (SNPs) in 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS) have been associated with elevated blood glucose levels following treatment with chlorthalidone and HCTZ in both African American and Caucasian populations.

A meta-analysis encompassing four studies with over 1,000 patients indicated that polymorphisms in the ACE and ADD1 genes influence blood pressure responses to HCTZ [89]. The ADD1 gene encodes α-adducin, a cytoskeletal protein involved in ion transport modulation, while the ACE gene encodes the angiotensin-converting enzyme, a key component of the renin–angiotensin system responsible for regulating body fluid volume and blood pressure. A meta-analysis by Choi et al. identified a significant association between the ACE II and DD genotypes and blood pressure changes (standard differences in means = 0.256; 95% CI, 0.109–0.403). Additionally, Sciarrone et al. reported that individuals with the II genotype demonstrated superior antihypertensive responses to hydrochlorothiazide compared to those with the DD genotype. A study conducted in the Han Chinese population suggested that this polymorphism modulates hydrochlorothiazide responses in a gender-specific manner; men with the DD genotype exhibited better antihypertensive responses than women with the II genotype. However, other studies did not confirm such associations (Suonsyrjä et al., 2009).

In the GenHAT (Genetics of Hypertension Associated Treatments) study, an ancillary investigation of the Antihypertensive and Lipid-Lowering Treatments to Prevent Heart Attack Trial (ALLHAT), researchers analyzed several candidate hypertension-related genes in 39,114 participants to identify potential gene variants affecting antihypertensive drug response. Findings from GenHAT indicated that the DD genotype of the ACE gene (rs1799752) does not influence blood pressure reduction or cardiovascular outcomes compared to the ID and II alleles. For the ADD1 Gly460Trp polymorphism (rs4961), a notable association was observed for the GlyGly versus GlyTrp genotypes (standard differences in means = 2.78; 95% CI, 0.563–4.99) and GlyGly versus TrpTrp genotypes (standard differences in means = 1.80; 95% CI, 1.38–2.22) [89]. Another study reported that carriers of the Trp allele for the Gly460Trp polymorphism in the ADD1 gene exhibited reduced baseline plasma renin activity and better antihypertensive responses to hydrochlorothiazide compared to Gly/Gly homozygotes. Glorioso et al. suggested that this polymorphism (rs4961) may affect renal sodium handling by altering ion transport across cell membranes.

Other research has implicated GNB3, which encodes the β3-subunit of the G-protein, as another gene potentially involved in responses to hydrochlorothiazide treatment. This family of proteins plays a role in signal transduction from membrane receptors to a variety of intracellular effectors. The presence of the T allele for the C825T (rs5443) polymorphism in the GNB3 gene is associated with an RNA splice variant lacking nucleotides 498–620 in exon 9, leading to structural alterations in the β3-subunit of the G-protein and modulation of signal transduction. Turner et al. reported that the T allele correlates with improved antihypertensive responses to hydrochlorothiazide, with a gene–dose-dependent effect. However, a larger study yielded conflicting results indicating that the association between the rs5443 polymorphism and hydrochlorothiazide responses requires further validation.

In a study examining the impact of single nucleotide polymorphisms (SNPs) on the response of 228 male patients of European descent to four classes of antihypertensive (anti-HTN) drugs, including hydrochlorothiazide (HCTZ), over 80 distinct polymorphisms were identified. However, a significant correlation was observed only for aldehyde dehydrogenase 1 family member 13 (ALDH1A3) and chloride intracellular channel 5 (CLIC5). The researchers proposed that other family members of the ALDH gene, such as ALDH1A2 and ALDH7, are associated with hypertension in African Americans, while ALDH2 is linked to blood pressure (BP) regulation in East Asian populations (Kato et al., 2011). Genome-wide association studies (GWAS) also identified an association between the SNP rs261316 in the ALDH1A2 gene and uncontrolled BP after treatment with a thiazide diuretic/β-blocker combination in white participants of the PEAR study, with similar findings confirmed in the INVEST study. Additional GWAS investigations have identified various loci associated with BP responses to HCTZ across different ethnic groups. In African American populations, SNPs within the lysozyme (LYZ), YEATS domain containing 4 (YEATS4), and fibroblast growth receptor substrate 2 (FRS2) genes on chromosome 12q15 were shown to influence HCTZ responses. African Americans carrying the ATC haplotype (comprising alleles for SNPs rs317689 (A), rs315135 (T), and rs7297610 (C)) exhibited better responses to HCTZ than individuals with the ACT or ATT haplotypes. Conversely, the PEAR study found that the ATT haplotype in African Americans was also associated with favorable HCTZ responses. Additionally, a reduction in YEATS expression was observed in African Americans who were CC homozygotes for SNP rs7297610, but not in T carriers, suggesting a connection between the YEATS variant and HCTZ response (Duarte et al., 2013).

A meta-analysis of six clinical trials within the International Consortium for Antihypertensive Pharmacogenomics Studies found a strong correlation between the hydroxy-delta-5-steroid dehydrogenase, 3 β- and steroid δ-isomerase 1 (HSD3B1) gene and BP response to HCTZ in white hypertensive individuals ($p < 2.28\times10^{-4}$). HSD3B1 encodes the 3β-hydroxysteroid dehydrogenase enzyme, critical in aldosterone and endogenous ouabain biosynthesis. Genetic variants in HSD3B1 were also linked to hypertension or BP

variation. The CC genotype at rs6203 was associated with hypertension prevalence and elevated BP values in various studies. Furthermore, Svensson-Farbon et al. demonstrated that a genetic polymorphism (rs4149601G/A) in the neural precursor cell expressed, developmentally down-regulated 4-like, E3 ubiquitin protein ligase (NEDD4L) gene generated a cryptic splice site. Numerous studies have shown that polymorphisms in NEDD4L influence salt sensitivity, plasma renin levels, and hypertension susceptibility. The NORDIL study, which included Caucasian hypertensive patients, found that the G allele downregulated the epithelial sodium channel (ENaC) and increased sodium reabsorption in the distal nephron, leading to hypertension development. The G allele was also associated with greater BP reductions in response to HCTZ compared to AA homozygotes. These findings were confirmed in the PEAR study. Additionally, McDonough et al. found that white hypertensive carriers of cumulative copies of the G-C haplotype (rs4149601 and rs292449) in NEDD4L responded better to HCTZ. However, this association was not observed in African Americans, indicating the need for further research to establish the relevance of these findings in treatment decisions(McDonough et al., 2013).

A meta-analysis of data from the PEAR-1, GERA-1, NORDIL, and GENRES studies identified genome-wide significance for rs16960228 (A/G) in the protein kinase C alpha (PRKCA) gene. Turner et al. reported that systolic and diastolic BP responses to HCTZ were consistently greater in European American carriers of the GACAA genotype compared to GG homozygotes, potentially due to higher baseline PRKCA expression associated with the A allele. In the Caucasian population, SNPs within the SH2B adaptor protein 3 (SH2B3—rs3184504), fibroblast growth factor 5 (FGF5—rs1458038), and early B-cell factor 1 (EBF1—rs45551053) were linked to BP responses to HCTZ monotherapy. The rs3184504 SNP in SH2B3 was associated with higher BP and increased hypertension risk in Caucasians. Carriers of the CC genotype responded better to antihypertensive medications, particularly atenolol, compared to TT and TC genotypes. GWAS studies also revealed that rs2273359 in the EDN3 region modulated systolic BP responses to HCTZ, with CG genotype carriers showing greater BP reductions than CC genotype carriers.

The PEAR and PEAR-2 studies suggested that genetic variants in protein phosphatase 1 regulatory subunit 15A (PPP1R15A), dual specificity phosphatase 1 (DUSP1), and FBJ murine osteosarcoma viral oncogene homolog (FOS) were associated with improved antihypertensive responses to thiazide diuretics, with upregulated gene transcription in responders. A GWAS analysis of two Italian cohorts (MIHYPHCTZ and PHSS) identified six variants predictive of systolic BP response and five variants predictive of diastolic BP response to HCTZ treatment in untreated Caucasians with elevated BP. The strongest effect on systolic BP response was linked to intronic polymorphisms in TET2 (rs12505746) and two SNPs in CSMD1 (rs7387065 and rs11993031)(Chittani et al., 2015). Further analysis found that rs10995 in the VASP gene (vasodilator-stimulated phosphoprotein) was a functional SNP associated with greater BP responses to HCTZ and increased VASP mRNA expression. Additionally, re-sequencing of chromosome 12q in the GERA and PEAR studies identified a novel missense SNP (rs61747221) in the BEST3 gene, with better antihypertensive responses reported in individuals with the AA+AG genotypes compared to GG carriers (Singh et al., 2018).

Ethnic differences in responses to ACE inhibitors and β-blockers suggest that hypertension development may involve distinct pathways across ethnic groups. Clinical evidence generally indicates that Black populations respond more effectively to diuretics and calcium channel blockers, whereas White populations exhibit similar responses across all drug classes (Padmanabhan et al., 2010).

Conclusion

Hypertension remains a critical global health challenge, significantly contributing to the burden of cardiovascular diseases. Despite advancements in antihypertensive therapies, variability in drug response remains a persistent issue. Genetic polymorphisms influence the pharmacological efficacy of key drugs, including diuretics, calcium channel blockers, ACE inhibitors, ARBs, and β-blockers. Emerging evidence highlights the role of single nucleotide polymorphisms (SNPs) in modulating drug responses through mechanisms involving ion transport, metabolic pathways, and receptor sensitivity. Furthermore, ethnic variations underscore the need for personalized approaches to hypertension treatment, as demonstrated by differing responses among Black, White, and Asian populations. While genome-wide association studies have provided valuable insights, further research is essential to refine clinical guidelines and integrate pharmacogenomics into routine practice. Addressing these complexities will pave the way for optimized and individualized therapeutic strategies, reducing the prevalence of uncontrolled hypertension and its associated complications.

References

Bhatnagar, V., Garcia, E. P., O'Connor, D. T., Brophy, V. H., Alcaraz, J., Richard, E., Bakris, G. L., Middleton, J. P., Norris, K. C., Wright, J., Hiremath, L., Contreras, G., Appel, L. J., Lipkowitz, M. S., & AASK Study Investigators. (2010). CYP3A4 and CYP3A5 polymorphisms and blood pressure response to amlodipine among African-American men and women with early hypertensive renal disease. *American Journal of Nephrology*, *31*(2), 95–103. https://doi.org/10.1159/000258688

Chittani, M., Zaninello, R., Lanzani, C., Frau, F., Ortu, M. F., Salvi, E., Fresu, G., Citterio, L., Braga, D., Piras, D. A., Carpini, S. D., Velayutham, D., Simonini, M., Argiolas, G., Pozzoli, S., Troffa, C., Glorioso, V., Kontula, K. K., Hiltunen, T. P., … Barlassina, C. (2015). TET2 and CSMD1genes affect SBP response to hydrochlorothiazide in never-treated essential hypertensives. *Journal of Hypertension*, *33*(6), 1301–1309. https://doi.org/10.1097/HJH.0000000000000541

Duarte, J. D., Turner, S. T., Tran, B., Chapman, A. B., Bailey, K. R., Gong, Y., Gums, J. G., Langaee, T. Y., Beitelshees, A. L., Cooper-Dehoff, R. M., Boerwinkle, E., & Johnson, J. A. (2013). Association of chromosome 12 locus with antihypertensive response to hydrochlorothiazide may involve differential YEATS4 expression. *The Pharmacogenomics Journal*, *13*(3), 257–263. https://doi.org/10.1038/tpj.2012.4

Eadon, M. T., Kanuri, S. H., & Chapman, A. B. (2018). Pharmacogenomic studies of hypertension: Paving the way for personalized antihypertensive treatment. *Expert Review of Precision Medicine and Drug Development*, *3*(1), 33–47. https://doi.org/10.1080/23808993.2018.1420419

He, F., Luo, J., Luo, Z., Fan, L., He, Y., Zhu, D., Gao, J., Deng, S., Wang, Y., Qian, Y., Zhou, H., Chen, X., & Zhang, W. (2013). The KCNH2 genetic polymorphism (1956, C>T) is a novel biomarker that is associated with CCB and α,β-ADR blocker response in EH patients in China. *PloS One*, *8*(4), e61317. https://doi.org/10.1371/journal.pone.0061317

Kamide, K., Asayama, K., Katsuya, T., Ohkubo, T., Hirose, T., Inoue, R., Metoki, H., Kikuya, M., Obara, T., Hanada, H., Thijs, L., Kuznetsova, T., Noguchi, Y., Sugimoto, K., Ohishi, M., Morimoto, S., Nakahashi, T., Takiuchi, S., Ishimitsu, T., … HOMED-BP study group. (2013). Genome-wide response to antihypertensive medication using home blood pressure measurements: A pilot study nested within the HOMED-BP study. *Pharmacogenomics*, *14*(14), 1709–1721. https://doi.org/10.2217/pgs.13.161

Kato, N., Takeuchi, F., Tabara, Y., Kelly, T. N., Go, M. J., Sim, X., Tay, W. T., Chen, C.-H., Zhang, Y., Yamamoto, K., Katsuya, T., Yokota, M., Kim, Y. J., Ong, R. T. H., Nabika, T., Gu, D., Chang, L., Kokubo, Y., Huang, W., … He, J. (2011). Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in East Asians. *Nature Genetics*, *43*(6), 531–538. https://doi.org/10.1038/ng.834

Laurent, S. (2017). Antihypertensive drugs. *Pharmacological Research*, *124*, 116–125. https://doi.org/10.1016/j.phrs.2017.07.026

Li, Y., Yang, P., Wu, S., Yuan, J., Shen, C., Wu, Y., Zhao, D., Ren, Q., Feng, F., & Guan, W. (2011). Gender-specific association between ACE gene I/D polymorphism and blood pressure response to hydrochlorothiazide in Han Chinese hypertensive patients. *Biochemical Genetics*, *49*(11–12), 704–714. https://doi.org/10.1007/s10528-011-9444-6

McDonough, C. W., Burbage, S. E., Duarte, J. D., Gong, Y., Langaee, T. Y., Turner, S. T., Gums, J. G., Chapman, A. B., Bailey, K. R., Beitelshees, A. L., Boerwinkle, E., Pepine, C. J., Cooper-DeHoff, R. M., & Johnson, J. A. (2013). Association of variants in NEDD4L with blood pressure response and adverse cardiovascular outcomes in hypertensive patients treated with thiazide diuretics. *Journal of Hypertension*, *31*(4), 698–704. https://doi.org/10.1097/HJH.0b013e32835e2a71

Oliveira-Paula, G. H., Luizon, M. R., Lacchini, R., Fontana, V., Silva, P. S., Biagi, C., & Tanus-Santos, J. E. (2017). Gene-Gene Interactions Among PRKCA, NOS3 and BDKRB2 Polymorphisms Affect the Antihypertensive Effects of Enalapril. *Basic & Clinical Pharmacology & Toxicology*, *120*(3), 284–291. https://doi.org/10.1111/bcpt.12682

Oliveira-Paula, G. H., Pereira, S. C., Tanus-Santos, J. E., & Lacchini, R. (2019). Pharmacogenomics And Hypertension: Current Insights. *Pharmacogenomics and Personalized Medicine*, *12*, 341–359. https://doi.org/10.2147/PGPM.S230201

Padmanabhan, S., Paul, L., & Dominczak, A. F. (2010). The Pharmacogenomics of Anti-Hypertensive Therapy. *Pharmaceuticals*, *3*(6), 1779–1791. https://doi.org/10.3390/ph3061779

Rimpelä, J. M., Kontula, K. K., Fyhrquist, F., Donner, K. M., Tuiskula, A. M., Sarin, A.-P., Mohney, R. P., Stirdivant, S. M., & Hiltunen, T. P. (2017). Replicated evidence for aminoacylase 3 and nephrin gene variations to predict antihypertensive drug responses. *Pharmacogenomics*, *18*(5), 445–458. https://doi.org/10.2217/pgs-2016-0204

Singh, S., Wang, Z., Shahin, M. H., Langaee, T. Y., Gong, Y., Turner, S. T., Chapman, A. B., Gums, J. G., McDonough, C. W., Bailey, K. R., Beitelshees, A. L., Cooper-DeHoff, R. M., Scherer, S., Boerwinkle, E., & Johnson, J. A. (2018). Targeted sequencing identifies a missense variant in the BEST3 gene associated with antihypertensive response to hydrochlorothiazide. *Pharmacogenetics and Genomics*, *28*(11), 251–255. https://doi.org/10.1097/FPC.0000000000000353

Suonsyrjä, T., Donner, K., Hannila-Handelberg, T., Fodstad, H., Kontula, K., & Hiltunen, T. P. (2010). Common genetic variation of beta1- and beta2-adrenergic receptor and response to four classes of antihypertensive treatment. *Pharmacogenetics and Genomics*, *20*(5), 342–345. https://doi.org/10.1097/FPC.0b013e328338e1b8

Suonsyrjä, T., Hannila-Handelberg, T., Fodstad, H., Donner, K., Kontula, K., & Hiltunen, T. P. (2009). Renin-angiotensin system and alpha-adducin gene polymorphisms and their relation to responses to antihypertensive

drugs: Results from the GENRES study. *American Journal of Hypertension*, *22*(2), 169–175. https://doi.org/10.1038/ajh.2008.343

Turner, S. T., Bailey, K. R., Schwartz, G. L., Chapman, A. B., Chai, H. S., & Boerwinkle, E. (2012). GENOMIC ASSOCIATION ANALYSIS IDENTIFIES MULTIPLE LOCI INFLUENCING ANTIHYPERTENSIVE RESPONSE TO AN ANGIOTENSIN II RECEPTOR BLOCKER. *Hypertension*, *59*(6), 1204–1211. https://doi.org/10.1161/HYP.0b013e31825b30f8

Vandell, A. G., Lobmeyer, M. T., Gawronski, B. E., Langaee, T. Y., Gong, Y., Gums, J. G., Beitelshees, A. L., Turner, S. T., Chapman, A. B., Cooper-DeHoff, R. M., Bailey, K. R., Boerwinkle, E., Pepine, C. J., Liggett, S. B., & Johnson, J. A. (2012). G PROTEIN RECEPTOR KINASE 4 (GRK4) POLYMORPHISMS: BETA-BLOCKER PHARMACOGENETICS AND TREATMENT RELATED OUTCOMES IN HYPERTENSION. *Hypertension*, *60*(4), 957–964. https://doi.org/10.1161/HYPERTENSIONAHA.112.198721

Yoon, S. S., Burt, V., Louis, T., & Carroll, M. D. (2012). Hypertension among adults in the United States, 2009-2010. *NCHS Data Brief*, *107*, 1–8.

Zanger, U. M. (2010). Pharmacogenetics—Challenges and opportunities ahead. *Frontiers in Pharmacology*, *1*, 112. https://doi.org/10.3389/fphar.2010.00112

Zuo, X., Zhang, W., Yuan, H., Barrett, J. S., Hua, Y., Huang, Z., Zhou, H., Pei, Q., Guo, C., Wang, J., & Yang, G. (2014). ABCB1 polymorphism and gender affect the pharmacokinetics of amlodipine in Chinese patients with essential hypertension: A population analysis. *Drug Metabolism and Pharmacokinetics*, *29*(4), 305–311. https://doi.org/10.2133/dmpk.dmpk-13-rg-127