Review Article

Personalized Hypertension Treatment: Genome-based Prescriptions

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ABSTRACT

Genetic polymorphism refers to the simultaneous occurrence of two or more genotypes in a population. Key genes related to hypertension involved in this phenomenon—such as the angiotensin-converting enzyme insertion (I)/deletion (D) variant (ACE I/D), β1-adrenergic receptor (ADRB1, Arg389Gly), cytochrome P450 3A5 (CYP3A5 *1/*3 alleles), and α-adducin (ADD1, Gly460Trp)—influence responses to antihypertensive medications, including angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEi), β-adrenergic blockers (β-blockers), calcium channel blockers (CCBs), and diuretics. Incorporating genotype-guided prescription planning using weighted multi-gene panels, healthcare providers can tailor antihypertensive therapy to each patient's genetic profile, eliminating the trial-and-error approach to prescribing antihypertensive medication. This precision medicine strategy can potentially enhance blood pressure control, reduce the risk of adverse side effects, and enhance overall treatment outcomes in hypertensive patients. Further research and clinical studies of these multi-gene algorithms could revolutionize hypertension management by offering personalized treatment.

Keywords: antihypertensive; Pharmacogenomics; polymorphisms; ACE inhibitors; Angiotensin II receptor blockers; β-blockers; Calcium Channel Blockers; diuretics

INTRODUCTION

There are 5 main classes of antihypertensive medication commonly used in U.S healthcare. Among them, angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEi) are first-line antihypertensive pharmacotherapy. Both target the renin-angiotensin-aldosterone system (RAAS)—a key regulator of blood pressure and sodium balance involving the kidneys, cardiovascular system, and central nervous system. The process begins with the liver releasing angiotensinogen into the bloodstream. The precursor protein undergoes two key reactions: first, renin, secreted by the kidneys, converts angiotensinogen into angiotensin 1, and angiotensin-converting enzyme (ACE) then converts angiotensin 1 into angiotensin II (Ang II). Ang II acts as the final effector by binding to the angiotensin II type 1 receptor (AT1R), which causes vasoconstriction and thus increases blood pressure. It also stimulates the release of aldosterone, which promotes sodium reabsorption, further increasing blood pressure. ARBs work by blocking Ang II from binding to the active site of

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AT1R, preventing Ang II from binding and narrowing blood vessels, thus lowering blood pressure. ACEi, on the other hand, stops the conversion of angiotensin I to Ang II, thereby reducing both vasoconstriction and aldosterone release. However, ARBs lower blood pressure with fewer side effects than ACEi because they inhibit the angiotensin pathway later in the signal cascade (1, 2).

Although not a first-line antihypertensive therapy, β-adrenergic antagonists, more commonly known as β-blockers, are a widely prescribed hypertension treatment. These drugs target β-adrenergic receptors, specifically β1 and β2 subtypes, which influence blood pressure through different mechanisms. β1 receptors are primarily located in the heart. When activated by epinephrine or norepinephrine, they increase heart rate, enhance the strength of the heart's contractions, and stimulate renin release—each of which raises blood pressure. Blocking β1 receptors slows the heart rate and reduces blood pressure. For this reason, selective β1-blockers are typically preferred in hypertension treatment. In contrast, β2 receptors are found in the lungs and skeletal muscles, promoting smooth muscle relaxation and vasodilation. This leads to increased lung airflow and enhanced blood flow to the skeletal muscles. Blocking β2 receptors can cause vasoconstriction and bronchoconstriction, potentially increasing blood pressure and posing respiratory risks. Nonselective β-blockers such as propranolol inhibit both β1 and β2 receptors, which can lead to undesirable effects like elevated vascular resistance and bronchospasm (3).

Calcium Channel Blockers (CCBs) and Diuretics are commonly used antihypertensive medications. CCBs lower blood pressure by blocking calcium from entering the cells of the heart and arteries. Without calcium, blood vessels relax and open, allowing blood to flow more easily and lowering blood pressure (4). Thiazide diuretics lower blood pressure by promoting the excretion of sodium and water. They work by inhibiting the sodium-chloride channel in the distal convoluted tubule of the kidneys, decreasing sodium reabsorption. This causes more sodium and water to be eliminated in the urine, reducing blood volume and blood pressure (5).

Despite the availability of multiple antihypertensive classes, the drug response rate remains only about 50% and resistant hypertension affects up to 20% of patients. This highlights the limitations of the traditional "one-size-fits-all" prescribing model, which relies on trial and error and contributes to poor blood pressure control and increased healthcare costs. A genomic approach is needed to address this variability and guide individualized treatment decisions (6).

A clear understanding of the mechanisms of action of each antihypertensive drug class is essential to assess how genetic polymorphisms influence individual responses to treatment—and, consequently, how that data can be translated into a weighted multi-gene algorithm for guiding prescription decisions.

Objectives of this review are threefold: 1) to summarize genetic polymorphisms influencing response to major antihypertensive drug classes, 2) to evaluate the clinical potential of weighted multi-gene algorithms, and 3) to discuss opportunities and challenges in implementing genome-based hypertension therapy.

METHODS AND METERIALS

This literature review search followed the criteria below to evaluate the potential of genotype-based therapy for hypertension. Studies were identified through PubMed using the keywords such as hypertension, genetics, polymorphisms, and antihypertensive medication. Criteria for inclusion required experimental studies on genetic polymorphisms correlating to antihypertensive medication drug metabolism, genotype-based prescriptions, and literature reviews on multi-gene panels. Search strategies included the use of boolean operators such as "and" and "or," which were used to find studies relating to antihypertensive medication metabolism and patient genotypes. For precise search strategies, this review used MeSH (medical subject headings) terms, a feature of PubMed that is used for indexing articles, using MeSH terms like hypertension/gene therapy paired with more specific keywords like genetic polymorphisms and ACE inhibitors for a precise query. Searched PubMed for studies published from January 2000 through March 2025. The filtered search option was implemented to limit results to clinical trials, literature reviews, and meta-analyses. All of these components are compiled in the advanced search.

RESULTS

Out of 100 studies initially found, 70 met the inclusion criteria. After the screening, 60% of those were selected based on relevance to gene hypertension therapy, resulting in 45 PubMed articles. Exclusion criteria involved studies unrelated to hypertension control or genetic applications. The final analysis

used the most relevant findings for gene therapy for hypertension.

WEIGHTED MULTI-GENE ALGORITHMS

The weighted multi-gene algorithm is built on limitations of monogenic studies, which often fail to account for the multiple genotypes and organ systems involved in hypertension. Weighted multi-gene panel algorithms for hypertension treatment analyze patients' DNA for genetic determinants associated with response to antihypertensive medication, enabling a more tailored and effective treatment approach.

Patients treated with the algorithm's top-recommended medication showed significantly better blood pressure control than those who were not. The difference between diagnosis and average blood pressure after one year was smaller in patients matched to their genetically optimal treatment (6).

In a pilot study, the weighted multi-gene algorithm assessed gene polymorphisms that encode proteins within the renal, vascular, and cardiac systems for their role in blood pressure drug response. 86 patients provided buccal swabs, underwent baseline assessments, and had their medical charts reviewed for blood pressure history. The genes examined included WNK rs1159744, SLC12A3, ADD1, ADRB2, and CYP2D6, which all encode proteins or drug-metabolizing enzymes related to renal sodium handling and cardiovascular function. A statistically significant blood pressure improvement was observed in patients who received the algorithm-recommended treatment (7).

Another study developed its algorithm by assigning weighted scores to each functional genotype, based on peer-reviewed evidence. The method utilized functional genotypes influencing blood pressure response to hypertension therapy identified by current literature, including 17 SNPs in 11 genes (*ADRB1*, *ADRB2*, *CYP2D6*, *WNK*, *SLCI2A3*, *SCNN1A*, ADD1, REN, AGT, ACE, and AGTR1). Weighting was determined by both functional significance and literature support. Each weighed genotype was input into the algorithm for a pairing assessment within and across organ systems, taking homozygosity and heterozygosity into account, and medication options were ranked from 1 to 4 in terms of predicted efficacy (6).

Beyond clinical effectiveness, the multi-gene approach is highly cost-efficient. Over three years, it reduces healthcare costs by 47%, with estimated savings of $6.3 billion from fewer patient evaluations, $908 million from optimized medication use, and $37.5 billion from avoiding preventable cardiovascular events (8).

To implement the algorithm, patients provide a buccal swab—a simple, non-invasive DNA collection method. The sample is analyzed by a pharmacogenetic laboratory for genetic markers linked to blood pressure regulation and drug metabolism. These genetic findings, combined with clinical data such as blood pressure history and baseline health metrics, allow for a highly individualized treatment plan. The test is typically conducted in specialized clinical labs, with an estimated cost of $300 to $1000 (9, 10).

GENETIC POLYMORPHISMS IN ANTIHYPERTENSIVE DRUG RESPONSE

Numerous studies have identified single-nucleotide polymorphisms (SNPs) in genes related to the vascular, cardiac, and renal systems that affect individual responses to antihypertensive therapy. These findings support the development of precision medicine, which uses genetic variations in drug targets and metabolizing enzymes to personalize treatment (11). Pharmacogenomic studies typically employ two approaches: candidate gene studies, which focus on associations within pre-specified genes, and genome-wide association studies (GWAS), which scan the entire genome for SNPs. These types of studies are helpful in identifying genetic polymorphisms that influence blood pressure response for genetically guided therapy for hypertension (12).

Genetic polymorphisms that influence response to ACEi and ARBs

The ACE gene encodes the angiotensin-converting enzyme, which converts angiotensin 1 into Ang II, the final effector in the RAAS pathway. A multitude of studies suggest genetic polymorphisms in the ACE gene may influence the response of RAAS to antihypertensive medication. Studies show that a polymorphism in this gene, the I/D of an Alu repeat in intron 16 (rs1799752), significantly affects response to ACEi treatment (enalapril or lisinopril), as demonstrated in a study of 1,069 Han Chinese men (13).

The 3 genotypes—D/D, I/D, and I/I—exhibit variable blood pressure reductions in response to ACEi treatment. Patients with the D/D genotype tend to show the most significant decrease in blood pressure in response to ACEi treatment (enalapril or lisinopril) relative to the I/D and I/I genotypes, as shown in a

study of 72 Malay men (14). Studies show that the reason for increased efficiency in ACEi treatment for D/D genotype patients is that the genotype is associated with a higher rate of ACE activity, increasing the effects of inhibition (11).

Interestingly, I/I genotype patients show a greater blood pressure-lowering response to ARBs such as irbesartan, which block Ang II binding to the AT1R, than those carrying the D allele (15). The conclusions in relation to ACEi medication are that the D/D genotype experiences the lowest blood pressure reduction, the I/D genotype has a moderate response, the I/I genotype has a minimal response, so ARB treatment is optimal. Multi-gene panels would consider whether the patient is a D/D, I/D, or I/I genotype to determine the most effective hypertension treatment.

It's important to consider that although the D/D genotype has been linked to higher blood pressure and improved ACEi responsiveness in some populations, other studies report no significant association. For example, no association was found among Slovenians, Buryats, Thais, Romany subjects and Slovaks, Cubans, Algerian population from Oran, and some Chinese minorities (Mongolians, Uyghurs, Yugurs) (15).

Studies have shown that ACEi has pleiotropic beneficial effects, including vasodilation effects from nitric oxide produced by endothelial NO synthase (NOS3). The vasodilatory effect of ACEi occurs via the promotion of nitric oxide production through the stimulation of the NOS3 (16). Genetic testing has identified polymorphisms in genes encoding proteins involved in ACEi-induced vasodilation linked to blood pressure response to enalapril in a study among 300 South African adults with hypertension (17). Various studies among white and black patients in 200-person cohorts have concluded that variations in the NOS3 gene that are responsible for receptivity to enalapril treatment are the NOS3-665A/T SNP (rs3918226). T-allele carriers show enhanced NO-mediated vasodilation and respond more favorably to enalapril, while A-allele carriers show a weaker response (18, 19). When calculating which antihypertensive treatment would be most efficient, a multi-gene panel would consider whether the patient has an A or T allele.

Since ARBs inhibit Ang II from binding to the AT1R, variations in the renal regulation of Ang II may influence ARB efficacy. Decreased expression of nephrin, a protein encoded by the NPHS1 gene, is associated with elevated Ang II levels. A missense SNP (rs38114995, a GLU117Lys) in NPHS1 is linked to differential responses to ARB therapy in a study with 300 Finnish men (20). This is another potential factor to be implemented into the multi-gene algorithm for a more precise selection of the appropriate antihypertensive medication for the patient.

Genetic polymorphisms that influence response to β-blockers

β-blockers are mainly designed to block the β1 receptor encoded by the β1-androgenic receptor gene (ARDB1). β1 receptor blockers are preferred for antihypertensive response because they reduce renin secretion, therefore decreasing blood pressure. Scientists have studied genetic variants that would influence resistance to β-blockers and found the ADRB1 Ser49Gly-Arg389Gly SNPs mediate signaling activity in the β1-androgenic receptor (21-23). For instance, patients with the Arg389Gly genotype have enhanced intracellular responses to β1-blockers, increasing β-blocker responsivity. This was shown in a case-control study of 292 hypertensive patients and 265 controls (24). Further investigation into the Arg398Gly polymorphism of the ADRB1 gene reveals that patients homozygous for the Arg allele (Arg398Arg) exhibit significantly lower daytime-diastolic blood pressure in response to metoprolol compared to those homozygous for the Gly allele, as confirmed in both a small (<100) Chinese cohort and a 926-ethnically diverse person Secondary Prevention of Small Subcortical Strokes genetic substudy. However, findings remain inconsistent. A meta-analysis in Chinese populations concluded that the association between Arg389Gly and hypertension risk is unclear, highlighting population-specific differences (25, 26). This suggests enhanced β-blocker sensitivity in Arg389Arg carriers. A weighted multi-gene panel can incorporate this genotype—along with the additional predictive value of homozygosity—to optimize antihypertensive drug selection and support more personalized β-blocker prescriptions.

Genetic polymorphisms that influence response to Calcium Channel Blockers

CCBs bind to receptors on calcium channels to inhibit calcium ions from entering cardiac or aortic cells, which relaxes blood vessels. The CYP3A5 enzyme is part of the cytochrome P450 family and is primarily expressed in the kidney, and is involved in the metabolism of drugs and endogenous substrates (27). Recently, through candidate gene analyses, CYP3A5 has been associated with blood pressure response in

humans. Many studies have hypothesized that genetic polymorphisms in the CYP3A5 gene affect endogenous cortisol metabolism in the kidneys, leading to increased sodium and water retention, which ultimately impacts blood pressure. In contrast to the functional CYP3A5 (*1) allele, a mutation in intron 3 of the gene creates a CYP3A5(*3) variant—this (*3) allele is designated as non-functional because it encodes for a truncated protein version of the CYP3A5 enzyme, inhibiting it from performing drug metabolism roles (28, 29). Since the CYP3A5(*3) polymorphism is nonfunctional, it does not cause increased sodium and water retention in the kidneys; thus, it is associated with lower blood pressure levels.*1 allele is frequent in patients with African ancestry, and *3 allele is dominant in European and Asian populations. When these genotypes were tested for responsivity to CCB treatment (almondine), they had differing responses. Studies showed higher almondine concentrations in the blood plasma of *CYP3A5**1 carriers than in CYP3A5(*3) carriers, concluding increased responsiveness to almondine for the *CYP3A5**1 carriers, as shown in a study of 40 healthy Korean males (30). To conclude, the response to CCB treatment was enhanced in carriers of the functional (*1) allele, causing more significant reductions in blood pressure than the CYP3A5(*3) variant. In contrast, a large meta-analysis (~10,000 white subjects) found no significant association between CYP3A5 rs76746 and hypertension, underscoring population-specific effects (29).

SNPs in genes encoding calcium ion channels also alter the antihypertensive response to CCB. The genes responsible for producing the specific proteins that CCB drugs target on the calcium ion channels are the calcium voltage-gated channel subunit alpha1 C (CACNA1C) gene, which encodes the alpha 1c-subunit of the L-type calcium channel, and the calcium voltage-gated channel subunit alpha1 D (CACNA1D) gene, which encodes the alpha 1d-subunit of the L-type calcium channel (31, 32). Genetic testing for the efficacy of CCB treatments in controlled and uncontrolled hypertensive patients found polymorphisms rs527974G/A within *CACNA1C* and rs312481G/A and rs3774426C/T within CACNA1D result in an active lowering of blood pressure reactivity to CCBs (33). Hence, prescriptions for blood pressure reduction can be optimized if these polymorphisms are considered for patients taking CCBs through a weighted multi-gene algorithm.

Another study with genetic samples from 5,979 patients residing in the United States and Puerto Rican patients evaluated the CACNA1C gene association with major adverse cardiovascular events such as stroke, myocardial infarction, and death among hypertensive patients. As a result, 3 genetic groups with defined outcomes to CCB therapy based on the CACNA1C SNP rs1051375 were identified. Group 1 was a homozygous AA rs1051375 genotype for whom CCB therapy is most beneficial, with a 46% reduction in cardiovascular events. The homozygous GG rs1051375 genotype made up group 2, where β-Blocker therapy is more beneficial. In group 3, CCB therapy and β-blocker therapy are equivocally beneficial to the heterozygous A/G rs1051375 genotype (34). The different genotypes for the CACNA1C SNP rs1051375 can be input into the weighted multi-gene algorithm for consideration in selecting a hypertension therapy drug.

Genetic polymorphisms that influence response to diuretics

Thiazide and thiazide-like diuretics lower blood pressure by inhibiting the sodium-chloride cotransporter in the distal convoluted tubule of the kidney, reducing sodium reabsorption in the kidneys. This leads to increased urine output and consequently lowers blood pressure (35).

The interconnection of the RAAS and the sodium reabsorption capacity of the renal tubule plays a coordinated role in response to diuretic therapy. The alpha-adducin (ADD1) and ACE gene polymorphisms can be evaluated for their influence on blood pressure response to sodium, due to their roles in activating the RAAS (via the ACE gene) and regulating renal sodium reabsorption (via the ADD1 gene). The ADD1 gene encodes alpha-adducin, a protein involved in renal ion transport, and the ACE gene encodes the angiotensin-converting enzyme part of the RAAS (36, 11). A meta-analysis of four studies involving over 1,000 Korean male patients assessed the pharmacogenetic influence of ACE I/D and ADD1 Gly460Trp polymorphisms on blood pressure responses to hydrochlorothiazide treatment. The analysis found an association between ACE and ADD1 gene polymorphisms and improved blood pressure responses to hydrochlorothiazide treatment. The ADD1 Gly460Trp and ACE I/D variants show synergistic effects: carriers of the I allele (ACE) and Trp allele (ADD1) have the greatest reduction in blood pressure on diuretic therapy, while Gly460Gly +DD individuals have the poorest response (37, 38).

Additionally, neural precursor cell expressed, developmentally down-regulated 4-like (NEDD4L), a

gene that reduces the expression of epithelial sodium channels, which regulate blood pressure by balancing sodium levels and blood volume, is associated with an antihypertensive response to both β-blocker and diuretic monotherapy (39). In the NORDIL (Nordic Diltiazem) study, 10,881 patients with hypertension, including those treated with β-blockers or diuretics, who are carriers of the G-allele in the NEDD4L rs4149601A/G polymorphism, experienced the most significant blood pressure reduction. Later, the carriers of the G-allele randomized to β-blockers and/or diuretics were at less risk of adverse cardiovascular events after 4.5 years of follow-up than patients homozygous for the AA genotype. To conclude, a weighted multi-gene panel could consider how the NEDD4L rs4149601 polymorphism affects the capability of β-blocker and/or diuretic-based antihypertensive treatment in blood pressure reduction and protection against cardiovascular disease. However, other studies have found no significant association between this polymorphism and the response to antihypertensive therapy. For example, a study involving hypertensive patients treated with diltiazem found that the NEDD4L rs4149601 polymorphism did not influence the efficacy of diltiazem-based antihypertensive treatment (40) (Table 1).

Table 1. Genetic polymorphisms in antihypertensive drug response

Gene	Drug Class	Mechanism	Clinical Impact	Population Notes
ACE (I/D, rs1799752)	ACE inhibitors (enalapril, lisinopril); ARBs (irbesartan) (1, 2)	Alters ACE enzyme activity (D/D = ↑ ACE activity) (11)	D/D → strongest ACEi response; I/I → better ARB response (13, 14)	mixed or no association in some Asian and European minorities (15)
NOS3 (rs3918226)	ACE inhibitors (1, 2)	Regulates NO-mediated vasodilation (16)	T-allele carriers → enhanced BP reduction on enalapril (17)	Supported in European & African cohorts; limited sample sizes (18, 19)
NPHS1 (rs38114995, Glu117Lys	ARBs (1, 2)	Encodes nephrin; regulates Ang II signaling (20)	Lys allele carriers show altered ARB response (20)	Observed in Finnish men; replication needed (20)
ADRB1 (Arg389Gly, rs1801253)	β-blockers (metoprolol) (3)	Modulates β1-adrenergic receptor signaling (21-23)	Arg389Arg → significantly lower BP; Gly carriers → weaker response (24-26)	Shown in Chinese and SPS3 multi-ethnic trial; some meta-analyses report no clear association (25-26)
****CYP3A5 (*1/3, rs776746)*	CCBs (amlodipine, verapamil) (4)	Alters CCB metabolism and renal cortisol handling (28-29)	*1 carriers → higher clearance, stronger BP reduction; *3 carriers → weaker response (29, 30)	*1 frequent in Africans; *3 dominant in Europeans/ Asians; meta-analysis (~10,000 whites) showed no significant association (29, 30)
CACNA1C (rs1051375)	CCBs / β-blockers (3, 4)	Encodes α1C subunit of calcium channel (31)	AA → best CCB response; GG → better β-blocker response; AG → intermediate (33, 34)	Validated in >5,000 (U.S. & Puerto Rican cohorts) (34)
ADD1 (Gly460Trp, rs4961) + ACE I/D	Thiazide diuretics (5)	Synergistic effect on renal sodium transport and RAAS (36)	I/Trp carriers → greatest BP reduction; Gly/Gly + D/D → weakest (37, 38)	Meta-analysis of >1,000 Korean patients supports the combined effect (37, 38)
NEDD4L (rs4149601 A/G)	Diuretics / β-blocker (3, 5)	Regulates ENaC expression, modulating sodium balance (39)	G-allele → strongest BP response and reduced CV risk (40)	NORDIL showed positive effect; other cohorts (e.g., diltiazem-treated) show no association (40)

DISCUSSION

Genetically guided therapy has the potential to revolutionize hypertension management and alleviate the significant economic burden that uncontrolled blood pressure imposes on the U.S. healthcare system (6). Although 70% of patients receive treatment for hypertension, only half achieve adequate control, resulting in approximately $51 billion in annual costs (41).

Research indicates that the average effectiveness of major classes of antihypertensive medications—including ACE inhibitors, ARBs, β-Blockers, CCBs, and diuretics—is only about 50%(39, 42). This costly trial-and-error approach often compels physicians to repeatedly combine or adjust medications, adding complexity and increasing healthcare usage (6, 43). However, incorporating genetic testing into hypertension treatment could reduce this trial-and-error process by identifying key genetic determinants, such as ACE (I/D), NOS3, NPHS1, ARDB1, ADRB2, CYP3A5, CACNA1C, CACNA1D, ADD1, and NEDD4L.

While genome-guided hypertension therapy shows great promise, it is essential to recognize the current limitations of pharmacogenomic research. High-throughput genotyping arrays offer incomplete coverage of pharmacogenes, detecting less than 85% of common variants and even fewer rare variants. This limitation can result in the potential underdetection of clinically significant alleles. Moreover, most studies rely on reference panels of European ancestry, which may limit the applicability of findings across diverse populations. Small sample sizes further diminish the statistical power of these studies (44).

These technological and methodological limitations underscore the need for further research before pharmacogenomics can be fully integrated into clinical hypertension management.

CONCLUSION

Drug response involves multiple genes, and hypertension as a polygenic trait complicates finding the ideal genotype. However, continued research in gene therapy could be the future of antihypertensive treatment. Implementing multi-gene panels that complete genetic polymorphism analysis to guide prescription enables healthcare providers to optimize treatment to the patient's genetic profile.*A*CEi (enalapril, lisinopril) and ARB (irbesartan) responses depend on the ACE gene insertion (I) or deletion (D) variant. The D/D genotype shows the least blood pressure reduction, I/D a moderate response, and I/I minimal response, with ARB therapy being most effective. β-Blocker (metoprolol) efficacy is influenced by ADRB1/ADRB2 polymorphisms: Arg389 responds well, while Gly489 carries higher cardiac risk if treated. The response to CCBs (verapamil, amlodipine) is linked to CYP3A5 variants; CYP3A51 yields the optimal reduction, whereas CYP3A53 responds less. For diuretics, ACE (I/D) combined with ADD1 Gly460Trp has a synergistic effect— I/Trp carriers achieve greater reduction than D/D or Gly/Gly genotypes. Future directions include using machine learning to integrate multi-omics data (e.g. genomic, epigenomic, transcriptomic), which can be used for predictive models to replace the incomplete high-throughput genotype array approach. High-throughput genotype arrays primarily focus on genetic variations. Integrating other omics data can compensate for this by incorporating dynamic changes in gene expression (transcriptomics) and epigenetic modification (epigenomics) that influence phenotype. Additionally, conducting larger multi-ethnic clinical trials to ensure generalizability is essential to improve genetic data. With these advances, genetically guided strategies can improve blood pressure control, minimize adverse effects, and optimize outcomes (45).

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CONFLICT OF INTERESTS

All authors declare no conflict of interest.

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