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Pharmacogenomics β-Blockers in Cardiovascular Disease: Implications for Blood Pressure and Clinical Outcomes

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Abstract

Hypertension is a chronic condition that increases the risk of cardiovascular disease and death. β-blockers, including atenolol, metoprolol, bisoprolol, and carvedilol, lower blood pressure by blocking adrenergic receptors. However, variations in response and side effects are often influenced by genetic differences that affect drug metabolism and action. This narrative review analyzes studies published between 2014 and 2024 in PubMed, ScienceDirect, and Google Scholar using keywords related to genetic variation, β-blockers, hypertension, pharmacogenetics, and polymorphisms. Original studies in English, clinical trials on genetic polymorphisms and β-blocker response were included; reviews and incomplete studies were excluded. Clinical outcomes included changes in systolic and diastolic blood pressure, heart rate, hypotension, aortic root z-score, LVOT gradient, NT-proBNP, and premature ventricular contractions, which were associated with polymorphisms in the *ADRB1, ADRB2, ACY3, FGD5, SLC4A1*, and *SLC25A31* genes. Metabolic outcomes, impaired fasting glucose, new-onset diabetes, and melatonin metabolite changes were associated with variants in *PRKCB*, *DPYS*, *PAH*, and *PLEKHH2*. Most data came from European and North American populations, with limited representation from Asia, limiting generalizability. These findings support the use of pharmacogenomics to personalize β-blocker therapy and improve hypertension management, despite challenges related to high costs, limited infrastructure, the lack of clinical guidelines, and population heterogeneity.

Keywords: β-blockers, Genetic polymorphisms, Hypertension, Pharmacogenomics, Precision medicine

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Farmakogenomik β-Blocker pada Penyakit Kardiovaskular: Implikasi terhadap Tekanan Darah dan Hasil Klinis

Abstrak

Hipertensi adalah kondisi kronis yang meningkatkan risiko penyakit kardiovaskular dan kematian. β-blocker termasuk atenolol, metoprolol, bisoprolol dan carvedilol, menurunkan tekanan darah dengan cara memblokir reseptor adrenergik. Namun, variasi respons dan efek samping sering dipengaruhi oleh perbedaan genetik yang memengaruhi metabolisme dan aksi obat. Ulasan naratif ini menganalisis studi dari PubMed, ScienceDirect, dan Google Scholar yang diterbitkan antara 2014 dan 2024 menggunakan kata kunci terkait variasi genetik, β-blocker, hipertensi, farmakogenetik, dan polimorfisme. Studi asli dalam bahasa Inggris, uji klinis tentang polimorfisme genetik dan respons β-blocker dimasukkan, sedangkan ulasan dan studi yang tidak lengkap dikecualikan. Hasil klinis meliputi perubahan tekanan darah sistolik dan diastolik, denyut jantung, hipotensi, *root z-score*, gradien LVOT, NT-proBNP, dan kontraksi ventrikel prematur, yang terkait dengan polimorfisme pada gen *ADRB1, ADRB2, ACY3, FGD5, SLC4A1*, dan *SLC25A31*. Hasil metabolik, termasuk glukosa puasa terganggu, diabetes baru onset, dan perubahan metabolit melatonin, terkait dengan varian pada gen *PRKCB, DPYS*, *PAH*, dan *PLEKHH2*. Sebagian besar data berasal dari populasi Eropa dan Amerika Utara, dengan representasi terbatas dari Asia, membatasi generalisasi. Temuan ini mendukung farmakogenomik dalam personalisasi terapi β-blocker dan perbaikan manajemen hipertensi meskipun terdapat tantangan dalam biaya yang tinggi, infrastruktur, kurangnya panduan klinis, dan variasi populasi.

Kata Kunci: β-blocker, Farmakogenomik, Hipertensi, Pengobatan presisi, Polimorfisme gen

1. Introduction

Hypertension is one of the main causes of several heart and blood vessel complications, such as coronary heart disease (CHD), heart failure (HF), metabolic syndrome, chronic kidney disease and sleep apnea.[1] Globally, hypertension contributes to a significant burden of morbidity and mortality. According to the World Health Organization (WHO), it is estimated that by 2025 more than 1,5 billion people will suffer from hypertension.[2] In 2019, the global prevalence of hypertension reached 33.1%, with higher rates among men than women (31.7%). Although this rate has declined in Europe since 1990, it has increased in the Western Pacific region (from 24% to 28%) and Southeast Asia (from 29% to 32%). In the Western Pacific region, the number of adults with hypertension has more than doubled, from 144 million in 1990 to 346 million in 2019.[3] Based on data from the Indonesian Health Survey (SKI), the prevalence of hypertension in Indonesia reached 30.8% based on blood pressure measurements. For the 18–59 age group, the prevalence of hypertension was 5.9%, while for those aged 60 and above, it reached 22.9%.[4] The high prevalence of undiagnosed and uncontrolled hypertension is partly due to the absence of specific clinical symptoms, which often leads to late diagnosis. In addition, low treatment effectiveness, low patient compliance, and access to health services also contribute to inadequate blood pressure control.[5–7] However, this problem is not solely caused by compliance or access to health services. The low effectiveness of some therapies can also be attributed to biological variability between individuals.[8] These findings suggest that differences in response to antihypertensive therapy are likely influenced not only by clinical and environmental factors, but also by underlying genetic variations.

Several hypertension guidelines have removed β-blockers from their position as first-line therapy for hypertension. However, β-blockers remain widely used in the management of hypertension, especially in patients with cardiovascular comorbidities such as angina pectoris, heart failure, heart rate control disorders, and post-myocardial infarction.[9] β-blockers have been extensively studied in pharmacogenomic research, particularly in relation to adrenergic receptors.[10] Pharmacologically, β-blockers work by inhibiting β-adrenergic receptors, particularly β1-adrenergic receptors (β1-AR), thereby reducing heart rate, myocardial contractility, and renin secretion. This mechanism not only lowers blood pressure but also provides protective benefits to the cardiovascular system.[11] In addition to lowering blood pressure, the clinical effectiveness of β-blockers is largely determined by their chronotropic and inotropic effects, especially in conditions such as heart failure and arrhythmia.[12] Genetic variations that affect β-adrenergic receptor signaling can influence not only blood pressure response but also heart rate control, myocardial contractility, and overall cardiovascular outcomes.

Hypertension is a multifactorial disease with a genetic component, where family genetic studies show that heritability accounts for approximately 30% to 50% of the variation in blood pressure between individuals.[13] Genome-wide Association Studies (GWAS) have identified various genetic loci associated with blood pressure regulation and the cardiovascular system.[14,15] But it also influences the large interindividual variability in antihypertensive treatment, opening up opportunities for pharmacogenomic research and personalized drug therapy.[16,17]

Genetic polymorphisms such as single nucleotide polymorphisms (SNPs), insertion/deletion (I/D), and structural gene variations can modify drug receptor targets, drug metabolism, and signal transduction pathways.[18–20] Although this approach is still commonly used in hypertension therapy, this strategy can delay the achievement of blood pressure targets and increase the risk of cardiovascular complications. Identifying genetic biomarkers that can predict response to β-blockers before therapy begins will provide significant clinical benefits. The use of genetic information, along with other clinical and demographic data, enables more precise therapy selection, improves drug effectiveness, and minimizes the risk of side effects.[21]

This article reviews genetic polymorphisms that influence the effectiveness of β-blockers in the treatment of hypertension and cardiovascular diseases, such as atenolol, metoprolol, bisoprolol, and carvedilol. By analyzing genetic variations in genes such as *ADRB1, ADRB2, ACY3, FGD5, SLC4A1, SLC25A31, DYPS, PLEKHH2, PRKCB*, and *PAH*, with a focus on genes associated with efficacy and side effects. This article also emphasizes the importance of precision medicine for personalized therapy based on genetic profiles to improve treatment effectiveness and reduce the risk of side effects, providing insights into a future based on precision medicine.

2. Methods

A narrative review approach was used to assess relevant scientific sources in various reliable databases. Data and information were collected from scientific databases Google Scholar, PubMed, and ScienceDirect. The selected sources focused on articles discussing the effects of genetic variation on

the effectiveness and control of blood pressure with β-blocker antihypertensive drugs. The literature search was conducted using a combination of keywords and Boolean operators (AND, OR). The main search string used in PubMed was: ("β-blocker" OR "beta blocker") AND ("hypertension") AND ("pharmacogenetics" OR "pharmacogenomics") AND ("gene variation" OR "polymorphism"). Medical Subject Headings (MeSH) terms, including "Hypertension," "Adrenergic beta-Antagonists," and "Pharmacogenetics," were also used in PubMed to increase the sensitivity of the search. Similar keyword combinations were adapted for ScienceDirect and Google Scholar. The search was limited to articles published between 2014 and 2024 and written in English.

Inclusion criteria included original research articles in English and clinical trials examining the relationship between genetic polymorphisms and response to β-blockers in hypertension. Review articles were excluded to avoid duplicating data that had already been summarized, and studies with incomplete data were excluded due to limitations in rigorously evaluating methodology and outcome parameters. Data extraction was performed by reviewing each eligible study and summarizing key variables, including study design, population characteristics, sample size, genetic polymorphisms and SNPs studied, type of β-blocker administered, clinical outcomes (such as changes in SBP/DBP, heart rate, cardiac structural parameters, and metabolic markers), as well as reported effect sizes. Data were extracted manually and synthesized to provide a structured overview of pharmacogenomic associations. As this review used a narrative approach, standardized data extraction forms and a formal double-blind review process were not applied.

Although formal bias assessment tools were not used due to the narrative review design, study quality was evaluated based on relevance to pharmacogenomic outcomes. Greater emphasis was placed on clinical trials, cohort studies, and genome-wide association studies (GWAS) to enhance the reliability of the synthesized evidence. Because this review followed a narrative methodology, a systematic review framework or formal bias assessment tools were not applied. Therefore, the possibility of selection bias and interpretive limitations cannot be completely ruled out.

3. Results

3.1. β-blocker

Beta-blockers are β-adrenergic receptor antagonists of the G protein-coupled receptor family, which are critical for regulating processes such as blood pressure, heart rate, airway reactivity, and central nervous system function. These drugs block the binding of norepinephrine and epinephrine to β-adrenergic receptors, thereby exerting sympatholytic effects.[22] Most β1 receptors are in the heart, β2 receptors in the peripheral vascular bed, bronchi, and pancreas, and β3 receptors in the bladder, gallbladder, adipose tissue, and intestines. Beta-blockers are classified into three generations (Figure 1). First-generation (non-selective) beta-blockers inhibit β1 and β2 receptors.[23] Second-generation cardio-selective beta-blockers target β1 receptors. Meanwhile, the third-generation non-selective beta-blockers also block alpha-adrenergic receptors, reducing vascular resistance and improving cardiac function.[23,24]

Historically, β-blockers have been recommended as one of the first-line treatment options for primary hypertension by the Joint National Committee (JNC) on the Detection, Evaluation, and Treatment of High Blood Pressure, from its first report in 1977 to its seventh report in 2003. However, Messerli et al. later raised concerns about this preference, citing a lack

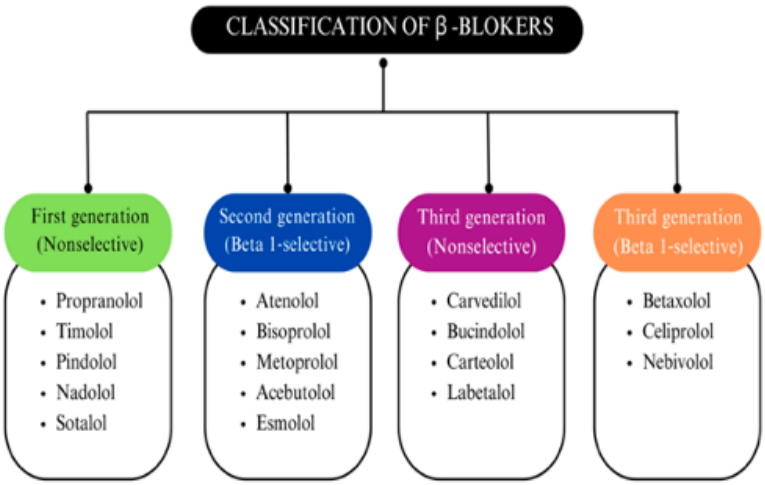

Figure 1. Classification of β-Blockers (designed by Biorender)

of evidence that β-blockers can reduce morbidity or mortality in patients with uncomplicated hypertension.[25] Current international guidelines prioritize other classes of antihypertensive drugs unless there are specific cardiovascular comorbidities. The principal therapeutic significance of β-blockers is attributed to their negative chronotropic and inotropic effects, which reduce heart rate, cardiac contractility, and systolic blood pressure, thereby diminishing myocardial oxygen consumption.[26] Therefore, the relevance of β-blocker pharmacogenomics extends beyond simply lowering blood pressure and includes modulation of cardiac function and autonomic regulation, reinforcing the potential of individually tailored β-blocker therapy in cardiovascular disease.[27]

3.2. Mechanism of Action of β-Blockers as Antihypertensives

Figure 2 illustrates the mechanism of action of β-Blockers beginning with the activation of beta-adrenergic receptors (β1 and β2) on cardiomyocytes, which are important for cardiac contraction via the neurotransmitter norepinephrine (NE) from the sympathetic nervous system.[28] These receptors activate adenylate cyclase (AC) via G proteins, converting ATP to cAMP. The increased cAMP activates protein kinase A (PKA), allowing calcium (Ca^{2+}) entry into cells, increasing intracellular Ca^{2+}, and inducing cardiac muscle contraction.[25,29,30] Beta-blockers work by inhibiting beta-1 and/or beta-2 receptors, thereby preventing norepinephrine from binding to and activating postsynaptic beta-adrenergic receptors in the heart and blood vessels. As a result, they decrease the heart rate (chronotropy), the force of myocardial contraction (systolic contraction), the conduction velocity (dromotropy), and the rate of myocardial relaxation (diastolic contraction).[31] Beta-blockers, while effective, are associatedwith side effects, including bradycardia, hypotension, fatigue, dizziness, nausea, constipation, and, in certain instances, sexual dysfunction.[32] Bronchospasm, although rare, can occur, especially in patients with asthma. Beta-blockers may worsen Raynaud's syndrome and mask the symptoms of hypoglycemia, therefore posing a risk to diabetic patients. Hyperglycaemia may also occur.[33]

3.3. Summary of Gene Polymorphisms Influencing β-Blocker Mechanisms

Based on Figure 3, the mechanism of action of β-blocker drugs in reducing blood pressure is influenced by multiple genetic variations that affect their effectiveness in treating hypertension. Identified genes are *ADRB1, ADRB2, ACY3, FGD5, SLC4A1, SLC25A31, DYPS, PLEKHH2, PRKCB,* and *PAH*, which affect the efficacy, side effects, and metabolic risks of β-blocker therapy. *SLC4A1, FGD5, DPYS, PLEKHH2, PRKCB*, and *PAH* are associated with glucose metabolism and are not directly related to blood pressure regulation. Although indications of a metabolic effect exist, the specific role of these genes in β-blocker response remains to be elucidated

3.4. Current Report on Gene Polymorphisms and Their Effects On B-Blocker Therapy

Changes in genes encoding receptors or proteins involved in the mechanism of action of β-blockers may affect the effectiveness and side effects of therapy.34 Previous studies have identified polymorphisms in *ADRB1, ADRB2, PRKCB, PAH, DPYS, PLEKHH2, FGD5, SLC25A31, SLC4A1*, and *ACY3* as associated with the response to β-blockers, including reductions

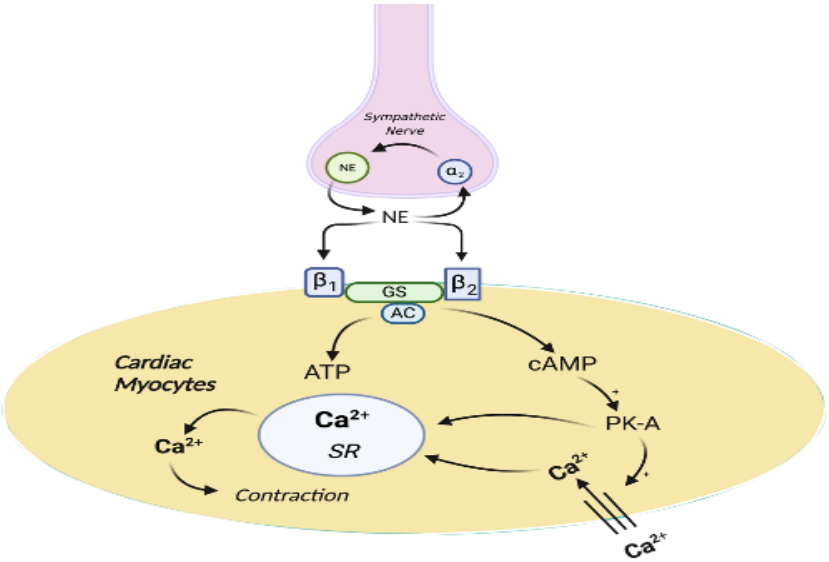

Figure 2. Mechanism of Action of Beta Blockers as Antihypertensives (design by Biorender)

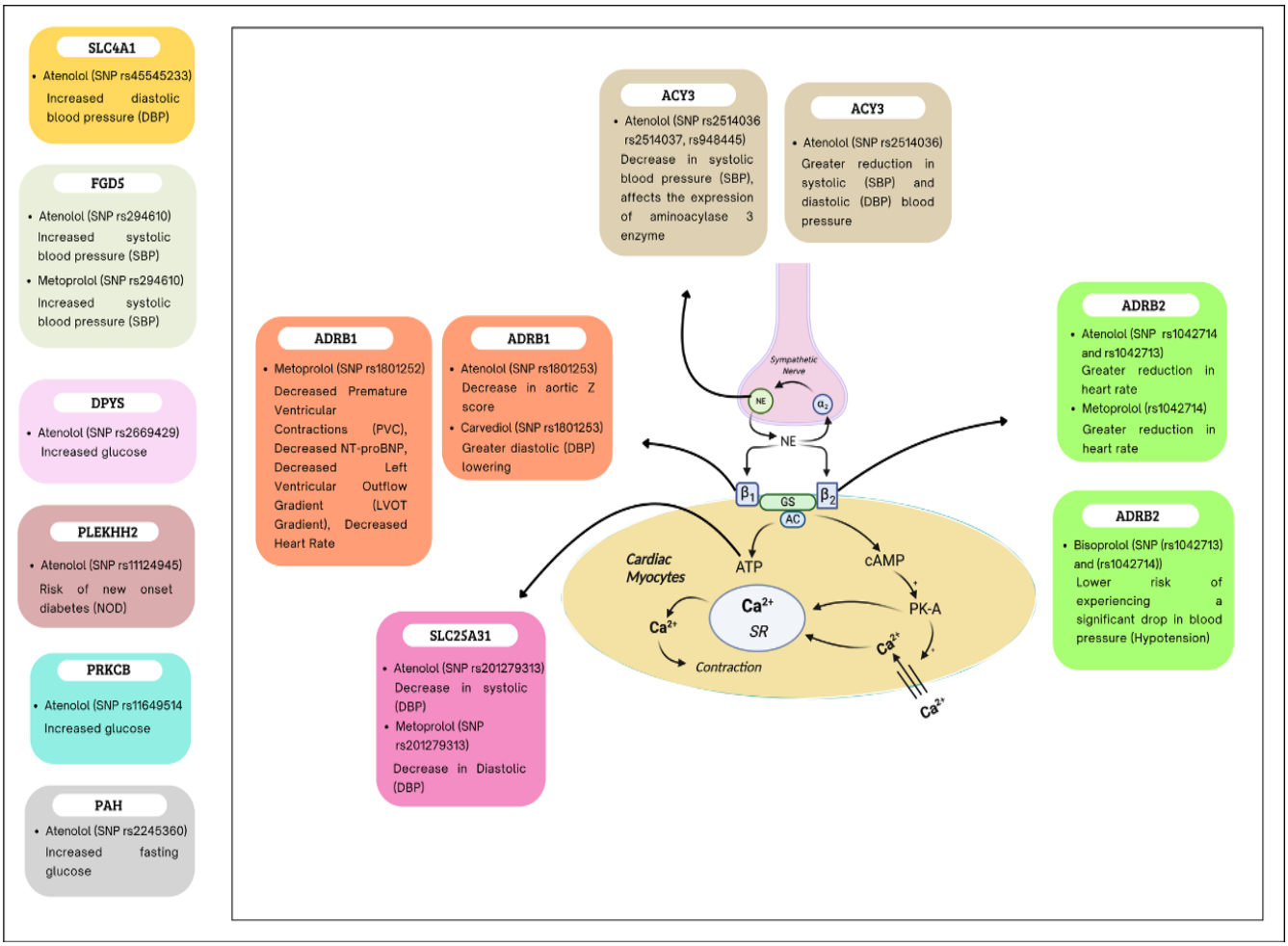

Figure 3. A Summary of the Mechanisms of Gene Polymorphisms Influencing β-Blocker Therapy

in blood pressure and heart rate, as summarized in Table 1.

4. Discussion

4.1. *ADRB1*, *ADRB2* gene polymorphism and the effect on β-blocker

β-adrenergic receptors (β-ARs), part of the G protein-coupled receptor superfamily, are crucial for cardiovascular function.50 In healthy hearts, the ratio of β1-AR to β2-AR is about 4:1, while β3-AR expression is minimal.51 The *ADRB1* and *ADRB2* genes encode β1-ARs and β2-ARs, respectively, which play a role in inotropic and chronotropic functions and regulate vascular and respiratory systems.[39] The Gly/Arg polymorphism at position 389 of *ADRB1*, which impacts G protein interaction and phosphorylation by GPCR kinases, plays an important role in receptor desensitization via β-arrestin.[52] This variation is significant in the response to β-blockers such as atenolol, making it a key area of focus in pharmacogenomic investigations.[53]

Research conducted by Raimoglou et al. (2024) revealed that the ADRB1 rs1801252 variant, causing a Serine (Ser) to Glycine (Gly) substitution at position 49, influences metoprolol response. Patients with the Ser49Ser genotype showed better outcomes, including reduced ventricular ectopic beats, LVOT gradient pressure, and NT-proBNP levels. Median PVCs dropped from 132 to 0 beats/day ($P<0.001$), and NT-proBNP decreased from 539 to 156 pg/mL. Meanwhile, Van Driest et al. (2020) studied the effect of the ADRB1-rs1801253 variant in Marfan syndrome patients treated with atenolol. The C>G (Arg389Gly) mutation impacts G protein binding.[54] The CC (Arg389/Arg389) genotype showed better β-blocker response, reducing aortic z-score by 0.20 per year versus 0.09 for CG or GG. This enhanced response is consistent with the higher signaling efficiency of the Arg389 variant, which results in stronger receptor G protein coupling and greater pharmacodynamic sensitivity to β-blockade. However, in patients with atrial fibrillation, CG or GG genotypes showed higher response in heart rate control, indicating that the clinical impact of *ADRB1* variants may differ across disease contexts. These findings support the potential

Table 1. A Summary of the Results on Gene Polymorphisms and Their Effects on β-Blocker Therapy

β-blockers	Gen	Polymorphism	Clinical Study Participants	Effect of Gene Variation	β-blockers Effect	Ref.
Atenolol	*ADRB1*	SNP rs1801253	White, non-Hispanic (American) (n=122)	Participants carrying the CC rs1801253 genotype showed a significantly greater improvement in aortic root z-score compared with 52 participants carrying the CG or GG genotypes.	Causing amino acid substitutions that reduce the coupling of the receptor with G proteins, thus affecting the response to beta-blockers.[35,36] Individuals with the CC genotype have a stronger response as the Arg389 receptor is more functional, while CG or GG genotypes show a weaker response.[34,37]	38
	ADRB2	SNP rs1042714 and rs1042713	United States of America. Hispanic subgroup PEAR (*Pharmacogenomics Evaluation of Antihypertensive Responses)* (n=757) (459 white skin and 298 dark skin) (INVEST (*International Verapamil SR-Trandolapril Study*) (n=1.401)	In white individuals, carriers of the rs1042714 C allele exhibited a decrease in heart rate, with a meta-analysis β of -0.95 beats per minute (bpm) and a meta-analysis P-value of 3×10^{-4}. Similarly, carriers of the rs1042713 A allele showed a reduction in heart rate, with a meta-analysis β of -1.15 bpm and a meta-analysis P-value of 2×10^{-3}	The A allele (Arg16) produces β2 receptors that are less susceptible to downregulation due to stimulation by agonists such as norepinephrine. β2 receptors remain available in sufficient numbers so that atenolol can bind and inhibit adrenergic signalling more effectively.	39
	FGD5	SNP rs294610	European Americans (*Pharmacogenomics Evaluation of Antihypertensive Responses*) (n=233)	Significantly associated with increased diastolic blood pressure (DBP) response to β-blockers in PEAR-2 study -2.70 mmHg and replicated -1.17 mmHg in PEAR study	FGD5 is involved in vascular remodelling through endothelial cell-specific apoptosis and vascular pruning, contributing to blood pressure regulation.[40]	40
	SLC4A1	SNP rs45545233	European Americans (*Pharmacogenomics Evaluation of Antihypertensive Responses*) (n=207)	DBP pressure increases the response of 4.57 mmHg on atenolol therapy.	SNP rs45545233 affects these responses by altering ion transport or fluid homeostasis, indirectly affecting blood pressure regulation.	40
	ACY3	SNP rs2514036	(LIFE) (S*candinavian and Finnish populations*): (n=467)	In heterozygous men (AG), there was a 5.5 mmHg greater decrease in systolic blood pressure (SBP) compared to AA homozygotes The reduction in diastolic blood pressure (DBP) was 1.9 mmHg greater for the AG genotype compared to AA	Genetic variation rs2514036 modifies *ACY3* expression, affecting catecholamine precursor metabolism, which may amplify or diminish the effects of atenolol on β1 receptors.	36
	PLEKHH2	SNP rs11124945	European Americans (N=552); Hispanics (N=471); African Americans (N=117)	G allele carriers have a lower risk for New-Onset Diabetes (NOD) A/A homozygotes have a higher risk for NOD	It affects the expression of the PLEKHH2 gene, which plays a role in actin stabilization and matrix adhesion in kidney podocytes. Carriers of the G allele, β1 receptor inhibition is more effective in reducing the risk of NOD than the A/A genotype due to differences in glucose metabolism or insulin sensitivity mediated by PLEKHH2.	42
	SLC 25A31	SNP rs201279313	African Americans; University of Florida, Emory University,	Monotherapy with mean reduction in Diastolic Blood Pressure (DBP) and Mayo Clinic	It alters the expression or regulatory function of the SLC25A31 gene was -9.3 mmHg	17

			(monotherapy n=150) (extended therapy n=141)	for deletion and -4.6 for wild-type.		
	PRKCB	SNP rs11649514	Caucasian; University of Florida Gainesville, Florida; Mayo Clinic Rochester, Minnesota; Emory University Atlanta, Georgia (n=232)	Therapy with atenolol caused an increase in glucose by 1.8 ± 10.1 mg/dl and a decrease in aMT6s by -4.5 ± 10.1 ng/mg. However, changes in aMT6s levels showed no correlation with changes in glucose after atenolol administration. In addition, SNP rs11649514 in the PRKCB gene was found to be associated with changes in glucose levels.	PRKCB plays a role in the melatonin-insulin regulatory pathway and may significantly contribute to atenolol-induced hyperglycemia in clinical settings	37
	DPYS	SNP rs2669429	Caucasian; Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) (n=462)	It affects the expression of enzymes involved in the production of β-alanine, which plays a role in glucose regulation. Individuals with the G allele showed increased glucose levels after Atenolol treatment compared to individuals without the carrier. Each copy of the G allele is associated with an increase in glucose levels by 2.76 mg/dL	It alters β-alanine production, affects glucose metabolism, and increases the risk of hyperglycemia during Atenolol therapy.	
	PAH	SNP rs2245360	European Americans; University of Florida; Gainesville; Emory University, Atlanta; Mayo Clinic, Rochester, MN (n=234)	The AA genotype showed the highest incidence of Impaired Fasting Glucose (IFG) at 41.7%, compared to the AG genotype at 15.2% and GG at 7.4%..	Disruptions in the PAH pathway affect insulin sensitivity and glucose metabolism, thereby contributing to impaired fasting glucose (IFG), especially in conditions of beta-blocker-induced dysglycemia after atenolol therapy. These mechanisms reflect the dysmetabolic pathways underlying drug effects and primary metabolic disturbances and the importance of pharmacometabolomics and pharmacogenomics approaches to understanding therapy response in greater depth.	44
Metoprolol	*ADRB1*	SNPS rs1801252	Turkey and England (Royal Brompton and Harefield Hospitals, London, UK) (n=147)	Metoprolol therapy in Hypertrophic cardiomyopathy (HCM) decreased the Premature Ventricular Contractions (PVC) 0 beats/day from 132 beats/day, a decrease in NT-proBNP 156 pg/mL from 539 pg/mL, a decrease in Left Ventricular Outflow Gradient (LVOT Gradient) 14 mmHg from 38 mmHg, a response to Heart Rate Decrease 66.7 ± 8.1 beats/min from 75.2 ± 10.8 beats/min.	Patients with homozygous Ser49 genotype are more responsive to beta-blocker therapy, possibly due to higher sensitivity to adrenergic stimulation.	45
		SNPS rs1801253 (Arg389Gly)	Han Chinese patients with essential hypertension	The CC genotype (Arg389Arg) showed a greater reduction in blood pressure than the GC or GG genotypes.	The antihypertensive response to metoprolol is better in patients with higher β1 receptor activity.	46

	ADRB2	SNP rs1042714 and rs1042713	United Stated of America; Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) (N= 368)	In white individuals, carriers of the rs1042714 C allele showed a meta-analysis β of -0.95 beats per minute (bpm), while carriers of the rs1042713 A allele had a meta-analysis β of -1.15 bpm	The A allele (Arg16) produces β2 receptors that are less susceptible to downregulation due to stimulation by agonists such as norepinephrine. β2 receptors remain available in sufficient numbers so that atenolol can bind and inhibit adrenergic signalling more effectively.	39
	SLC2 5A31	SNP rs201279313	African Americans; University of Florida, Emory University, dan Mayo Clinic (monotherapy n=168)	On metoprolol therapy, the reduction in DBP was -9.6 mmHg for heterozygotes and -4.8 mmHg for wild-type.	Alters the expression or regulatory function of the SLC25A31 gene which plays a role in the regulation of mitochondrial membrane potential. However, the exact mechanism and functional basis of this relationship still require further research.	17
	FGD5	SNP rs294610	European Ancestry (Europe) (n = 201)	Significantly associated with increased diastolic blood pressure (DBP) response to β-blockers in PEAR-2 study -2.70 mmHg and replicated -1.17 mmHg in PEAR study	SNP rs294610 in FGD5 enhances response to β-blockers, which may be due to amelioration of endothelial dysfunction facilitated by the gene's molecular pathway.	40
Bisoprolol	*ADRB2*	SNP Gly16Arg (rs1042713) dan Glu27Gln (rs1042714)	Granada, Spain (n=285)	The G (Glu) allele of the ADRB2 gene (rs1042714; Glu27Gln) has a protective effect against hypotension induced by beta-blocker use. In addition, the GG genotype of ADRB2 (rs1042713; Gly16Arg) was also shown to prevent hypotensive events, with OR (95% CI) = 0.49 (0.28 - 0.88).	Gly16Arg (rs1042713): Arg16 causes faster receptor downregulation, thus reducing the response to endogenous ligands such as epinephrine and norepinephrine. Expression of β2 receptors is higher, which results in more "hypofunctional" receptors. and decreases vasodilatory effects.	35
	ACY3	SNP rs2514036	Finland GENRES (Genomic and Metabolic Associations in Response to Antihypertensive Medications)(n=228) LIFE (Losartan Intervention For Endpoint reduction in hypertension) (n=377)	In heterozygous (AG) men, there was a 5.4 mmHg greater reduction in systolic blood pressure (SBP) compared to AA homozygotes The decrease in diastolic blood pressure (DBP) was 1.9 mmHg greater for the AG genotype compared to AA	SNP rs2514036 may affect the metabolism of substrates such as phenylalanine involved in the catecholamine synthesis pathway, thus affecting the efficacy of bisoprolol.	36
	ACY3	SNPs rs2514036, rs948445, and rs2514037	Finland; GENRES (Genetics of Drug Responsiveness in Essential Hypertension) (n=228)	The G/A allele was associated with a decrease in systolic blood pressure by approximately 5.4 mmHg and diastolic blood pressure by 3.1 mmHg.	These SNPs affect the expression or activity of the aminoacylase 3 enzyme, which regulates the metabolism of amino acids such as phenylalanine and tyrosine. This may impact the availability of neurotransmitters such as dopamine and norepinephrine, which are crucial for blood pressure regulation.[47,48]	48
Carvediol	ADRB1	Arg389Gly Gly389Gly	China (n=87)	Patients with ADRB1 Arg389 homozygotes had a four-fold greater increase in dias-tolic blood pressure (DBP) compared to ADRB1 Gly389 homozygous patients (10.61 vs 2.62 mmHg)	The Arg389 variation increases the ability of β1-adrenergic receptors to bind agonists such as carvedilol, mediates higher adenylate cyclase activity, and strengthens the vasodilatory	49

	In addition, ADRB1 omozygosity was also a significant predictor of response. Patients with the Gly49Arg389/Ser49Arg389 haplotype showed a 5.7 times greater reduction in systolic blood pressure (SBP) than patients homozygous for the Ser49Gly389 haplotype (16.11 vs 2.83 mmHg).	and blood pressure lowering effects compared to Gly389 which has lower affinity.	49

role of *ADRB1*-rs1801253 as a predictive marker for β-blocker responsiveness. These findings highlight the importance of pharmacogenetics. The CC (Arg389/Arg389) genotype shows higher receptor activity and better response to β-blockers than CG or GG (Arg389/Gly389 or Gly389/Gly389), which have lower activity. However, in patients with atrial fibrillation, CG or GG genotypes showed higher response in heart rate control.[38] This variability emphasizes the importance of considering pharmacogenetic variants in specific patient populations. In Marfan syndrome, the CC genotype showed a decrease in aortic z score of 0.20 per year, more significant than CG or GG, which only decreased by 0.09 per year.[38] These findings support the use of *ADRB1*-rs1801253 to guide the best therapy for Marfan syndrome patients

Research conducted by Shahin et al. (2019), showed that genetic variants rs1042714 and rs1042713 in the *ADRB2* gene are crucial for the response to atenolol and metoprolol. Individuals with the C allele on rs1042714 had a decrease in heart rate of -0.95 bpm (P=3×10-4), while carriers of the A allele on rs1042713 showed a decrease of -1.15 bpm (P=2×10-3). The A allele (Arg16) produces β2 receptors that are less susceptible to downregulation by agonists such as norepinephrine, thus allowing atenolol to be more effective in inhibiting adrenergic signaling.[39] The significant reduction in basal (from 75.2 ± 10.8 bpm to 66.7 ± 8.1 bpm) and maximum (from 118.9 ± 17.2 bpm to 106.9 ± 13.4 bpm) heart rates (P < 0.001) suggests that variations in β2 receptors may increase the effectiveness of β-blockers. In addition, previous studies have also shown that β1 receptor polymorphisms, such as substitutions at positions 49 and 389, affect the response to β-blockers. Raimoglou et al. (2024) reported that patients with the Ser49 homozygous genotype showed a significant reduction in mean heart rate after therapy, making this group more responsive to adrenergic stimulation and β-blocker therapy.[45]

Research conducted by Castaño-Amores et al. (2023) studied that patients with the GG rs1042713 genotype (Gly16Gly) had a 51% lower risk of hypotension (OR 0.49) compared to A allele carriers (Arg). The GG genotype (Glu27Glu) at rs1042714 (Glu27Gln) further reduced hypotension risk by 86% (OR 0.14).[35] Research conducted by Si et al. (2014) showed that the Arg389 polymorphism in the *ADRB1* gene affects the diastolic blood pressure (DBP) lowering response in patients receiving carvedilol. Patients with the Arg389Arg genotype showed a greater reduction in DBP (10.61 vs. 2.62 mmHg) than patients with the Gly389Gly genotype. Haplotype analysis also showed that the Gly49Arg389/Ser49Arg389 combination resulted in a more significant reduction in DBP (16.11 vs. 2.83 mmHg) than the Ser49Gly389 haplotype. The Arg389 variation increases β1-adrenergic receptor affinity to agonists such as carvedilol and adenylate cyclase activity, whereas Gly389 has lower affinity and activity. These polymorphisms affect drug binding and downstream signaling pathways that regulate vasodilation and blood pressure lowering.[49]

Further supporting the pharmacodynamic relevance of *ADRB1* polymorphisms, a prospective study in Chinese patients with essential hypertension treated with metoprolol for 12 weeks demonstrated that the *ADRB1* 1165G>C (Arg389Gly) polymorphism was independently associated with antihypertensive response. Patients homozygous for the mutant CC genotype showed significantly better systolic blood pressure reduction compared to heterozygous individuals, whereas CYP2D6 polymorphisms did not significantly influence treatment outcomes. Importantly, no interaction between *ADRB1* and CYP2D6 variants was observed, reinforcing that receptor-level genetic variation plays a more substantial role in β-blocker efficacy than metabolic variability in this population.[46]

4.2. *ACY3* gene polymorphism and the effect on β-blocker

Several polymorphisms in the *ACY3* gene, particularly rs2514036 (A>G), rs948445 (T>C), and rs2514037 (G>A), have been associated with variability in blood pressure response to β-blocker therapy. Among these, rs2514036 has shown the most consistent association with systolic and diastolic blood pressure reduction in patients treated with atenolol and bisoprolol. The *ACY3* gene encodes the enzyme aminoacylase 3, which plays a role in the deacetylation of compounds such as N-acetyl-phenylalanine to phenylalanine and

N-acetyl-tyrosine to tyrosine.[36] Catecholamines are synthesized through a series of enzymatic reactions that begin with the amino acid tyrosine in certain cells.[55] Catecholamines are synthesized from tyrosine through catalysis by the enzyme tyrosine hydroxylase, which produces DOPA. DOPA then undergoes a series of reactions to form dopamine, norepinephrine, and epinephrine.[56] In the cardiovascular system, epinephrine and norepinephrine increase cardiac output and blood pressure. The highest expression of *ACY3* in mice is found in the kidney, followed by the liver, heart, and brain.[36] In humans, its expression is found in neurons and the adrenal medulla. *ACY3* is thought to play a role in blood pressure regulation through tissue-specific expression patterns, its influence on catecholamine metabolism, and its relationship with plasma levels of phenylalanine and N-acetyl-phenylalanine.[36] Catecholamines from the adrenal medulla, including norepinephrine, which causes arterial vasoconstriction, have an important role in the neurohormonal regulation of blood pressure and hypertension.[53]

Rimpela et al. (2017) studied the SNP rs2514036 genetic variation in the *ACY3* gene that showing men with the G variation in this SNP experienced a greater reduction in systolic (SBP) and diastolic (DBP) blood pressure than men with the A variation when using atenolol and Bisoprolol. This variation resulted in a significant reduction in SBP of up to 5.5 mmHg in men, suggesting an interaction between sex and DBP of up to 1.9 mmHg, significantly reducing cardiovascular disease risk.[57] Hiltunen et al. (2015) identified three SNPs in the *ACY3* gene linked to blood pressure reduction in bisoprolol users. Rs2514036 is located in an upstream regulatory region, rs2514037 is intronic, and rs948445 is a missense variant (Arg8Gln), suggesting potential effects on gene regulation or enzyme activity. SNP rs2514036 (A>G), rs948445 (T>C), and rs2514037 (G>A) affect the aminoacylase 3 enzyme, impacting neurotransmitters like dopamine and norepinephrine that regulate blood pressure.[47] Patients with the G/A genotype exhibited reductions of 5.4 mmHg systolic and 3.1 mmHg diastolic pressure. SNPs rs2514036, rs948445, and rs2514037, found near the *ACY3* gene on chromosome 11, showed genome-wide significance. Rs2514036 is in an upstream regulatory region, rs2514037 is intronic, and rs948445 is a missense variant (Arg8Gln). *ACY3*, abundant in renal proximal tubules and less so in the brain and heart, deacetylates mercapturic acid, but its precise mechanism in blood pressure regulation remains unclear, necessitating further research.[48]

4.3. *FGD5* gene polymorphism and the effect on β-blocker

Genetic variants in the *FGD5* gene have been associated with blood pressure regulation and vascular response to antihypertensive therapy. Several SNPs located in regulatory regions or introns of the *FGD5* gene have been associated with variations in endothelial function and response to treatment. Given the central role of endothelial integrity in the pathogenesis of hypertension, these polymorphisms may influence individual response to β-blocker therapy.[58]

FGD5 (*FYVE, RhoGEF*, and *PH Domain Containing 5*) is a Rho GTP-binding protein expressed on vascular endothelial cells and plays a role in trafficking and VEGFR2 receptor function.[59] This protein contains the tandem Dbl-PH domain of *RhoGEF* and the FYVE and PH domains at its terminals. *FGD5* is thought to play a role in the development of hypertension through its influence on the vascular repair process, which is a key factor in the onset of hypertension. Endothelial dysfunction is one of the key mechanisms in the pathogenesis of hypertension.[60] β-blockers not only reduce sympathetic activity but can also improve endothelial function and reduce vascular dysfunction.[61] β-blockers are known to improve endothelial function through modulation of oxidative stress pathways and increased nitric oxide (NO) bioavailability.62 Because *FGD5* is involved in the regulation of angiogenesis and endothelial cell stability via the VEGFR2 pathway, genetic variations in *FGD5* may influence the extent to which vascular function improves during β-blocker therapy.[40,59]

Mouse studies have shown that *FGD5* is involved in the regulation of apoptosis in certain endothelial cells, which affects changes in blood vessel structure.[40] In vitro studies also support its role in the proangiogenic action of endothelial growth factor, indicating its involvement in vascular disorders such as hypertension. Additionally, previous studies have shown that β-blockers can ameliorate endothelial dysfunction and vascular mechanisms that play a role in their blood pressure-lowering effects. Therefore, *FGD5* polymorphism may influence the degree of vascular function improvement and blood pressure reduction during β-blocker use. However, further research is needed to understand the functional role of SNPs in the *FGD5* gene regarding β-blocker therapy response.[59]

4.4. *SLC4A1* gene polymorphism and the effect on β-blocker

SLC4A1 (*Solute Carrier Family 4 Member 1*) is a gene encoding the AE1 protein, which facilitates the exchange of chloride (Cl^-) and bicarbonate ions (HCO_3^-) at the plasma membrane of erythrocytes

and alpha intercalar cells in the kidney.[63]

Singh et al. (2019) found that the rs45545233 variant in the *SLC4A1* gene was significantly associated with reduced blood pressure in patients taking β-blockers. This gene is also associated with anion transport and major expression in erythrocyte membranes and renal tubules for chloride-bicarbonate exchange, as well as glucose and water transport.[40] Furthermore, Singh et al. (2019) showed that the genetic variants or (SNPs) in the *SLC4A1* gene, an allele change from T to C, are associated with a worse response to atenolol. Individuals carrying the C allele showed decreased effectiveness of atenolol, i.e. an increase in DBP by 4.57 mmHg showing very high significance.

4.5. SLC25A31 gene polymorphism and the effect on β-blocker

The *SLC25A31* (*Solute Carrier Family 25 Member 31*) gene encodes the ADP/ATP translocase 4 protein, which plays a role in facilitating the exchange of ADP and ATP in the mitochondrial membrane and regulating mitochondrial membrane potential.[17] This protein has an important role in maintaining cellular energy balance and metabolic processes. The mechanism of SNP rs201279313 in the SLC25A31 gene or its involvement in the blood pressure response to β-blockers remains unclear. Data from HaploReg shows that this variant is not highly related to other variants in the African population according to the 1000 Genomes database but is known to affect 14 regulatory motifs, such as Evi-1_4, Fox, and HDAC2_disc6. Further research is needed to understand the functional mechanisms of these associations.[17] Research by Gong et al. (2016) showed that the genetic variant *SLC25A31* (rs201279313) plays an important role in blood pressure response to atenolol and metoprolol. Atenolol monotherapy resulted in a mean reduction in diastolic blood pressure (DBP) of -9.3 mmHg in patients with the deletion genotype compared to -4.6 mmHg in the wild-type genotype. On adjunctive therapy of atenolol after hydrochlorothiazide, the reduction in DBP was recorded at -9.7 mmHg for the deletion genotype and -6.4 mmHg for the wild-type. Meanwhile, on metoprolol therapy, the decrease in DBP reached -9.6 mmHg in heterozygous patients and -4.8 mmHg in wild-type. These results suggested that the rs201279313 variant modulates the effectiveness of β-blockers in reducing diastolic blood pressure.

4.6. *DPYS* gene polymorphism and the effect on β-blocker

SNP rs2669429 is found in the first intron of the *DPYS* (*Dihydropyrimidinase*) gene, which encodes the enzyme *dihydropyrimidinase* (DHP). DHP plays a role in the reductive breakdown of pyrimidines and catalyzes the second step in the conversion of uracil to β-alanine.[43] Amino β-alanine was significantly associated with changes in glucose after treatment with atenolol. A gene in the β-alanine pathway (DPYS) was identified and correlated with glucose response from genomic studies. β-alanine has previously been associated with diabetic status.64 SNP rs2669429 modulates *DPYS* activity, affecting β-alanine production, which impacts energy metabolism and glucose homeostasis, thus affecting the effectiveness and side effects of β-blockers.

de Oliveira et al. (2016) found two important findings based on the metabolomics and genomics studies. Baseline β-alanine levels were associated with increased glucose after atenolol treatment. Linear regression analysis showed that higher β-alanine levels were associated with an increase in fasting glucose after treatment, showing significant results. In addition, SNP rs2669429 in the *DPYS* gene was also associated with increased glucose, where carriers of the G allele had an increased glucose of 2.76 mg/dL, as well as the group of participants who received atenolol as adjunctive therapy, showing statistical significance. These findings suggest that genetic and metabolic factors may predict susceptibility to atenolol-induced hyperglycemia

4.7. *PLEKHH2* gene polymorphism and the effect on β-blocker

PLEKHH2 (*Pleckstrin Homology Domain Containing Family H Member 2*) gene plays a role in actin stabilization and matrix adhesion, and is found in the context of renal podocyte function.[63] SNPs in *PLEKHH2* have been associated with diabetic nephropathy. Chang et al. (2016) explored genetic interactions with antihypertensive treatment and the risk of new-onset diabetes (NOD). SNP rs11124945 in the *PLEKHH2* gene showed that G allele carriers treated with β-blockers (atenolol) had a lower risk of NOD compared to those on calcium channel blockers (CCBs), with an OR = 0.38 ($P = 4.0 \times 10^{-5}$). In contrast, individuals with the A/A genotype on β-blockers had a higher NOD risk than those on CCBs (OR = 2.02, $P = 2.0 \times 10^{-4}$). *Expression Quantitative Trait Loci* (eQTL) analysis revealed that SNP rs11124945 affects gene expression in tissues related to glucose metabolism, supporting its relevance to NOD. The G allele lowers the NOD risk on β-blockers, while the AA genotype increases the risk compared to CCB therapy. In metabolic conditions, insulin enhances microvascular perfusion (capillary recruitment) in skeletal muscle and subcutaneous adipose tissue, increasing blood flow, especially after meals or physical exercise.65 This variation, therefore, influences the risk of new-

onset diabetes (NOD) after atenolol therapy, with the G allele decreasing the risk of β-blockers and the AA genotype increasing the risk versus calcium channel blockers (CCBs).

4.8. *PRKCB* gene polymorphism and the effect on β-blocker

Among the genetic variations studied in relation to the metabolic effects induced by β-blockers, the *PRKCB* rs11649514 polymorphism has emerged as a potential determinant of glucose response. This SNP has been associated with different changes in fasting glucose levels during atenolol therapy, suggesting genotype-dependent modulation of drug-induced dysglycemia.[42] Given the involvement of *PRKCB* in insulin signaling and melatonin-regulated metabolic pathways, genetic variation at this locus may alter individual susceptibility to β-blocker-related glucose homeostasis disturbances.[37]

PRKCB (*Protein Kinase C Beta*) encodes two major isoforms of protein kinase C (PKC) beta, namely PKCβ 1 and PKCβ. PKC is involved in melatonin downstream signaling, including the melatonin-insulin regulatory pathway.[66,67] The melatonin receptor signaling pathway plays an important role in an individual's risk of glucose dysfunction.[67] PKCβ also plays a role in regulating insulin signaling and insulin resistance.[68] Although the functional consequences of SNP rs11649514 are not yet fully understood, the analysis showed significant differences in glucose response to atenolol monotherapy based on genotype. Individuals with genotypes A/A or A/C experienced greater glucose elevation compared to genotypes C/C. In the group receiving atenolol with hydrochlorothiazide (HCTZ), a similar effect was seen but with a smaller effect size and not statistically significant. This is likely due to HCTZ being known to worsen glucose regulation and increase the risk of diabetes mellitus.[69] Therefore, the genetic influence of SNP rs11649514 on glucose regulation may be inhibited by combination therapy, indicating the need for further research to understand the specific mechanism.

Research by Chang et al. (2016) showed that there was no correlation between changes in aMT6s and glucose after treatment. At SNP rs11649514 in the PRKCB gene, individuals with the A allele (A/A or A/C) had a greater increase in glucose (5.7 ± 1.5 mg/dL) than C/C individuals (0.7 ± 0.7 mg/dL). The decrease in aMT6s was also smaller in individuals with the A allele (1.87 ± 1.97 ng/mg) compared to C/C (5.35 ± 0.76 ng/mg). This SNP is associated with changes in glucose levels ($P=1.0\times10^{-4}$) and plays a role in the melatonin-insulin regulatory pathway.

4.9. *PAH* gene polymorphism and the effect on β-blocker

The *PAH* gene encodes the enzyme phenylalanine hydroxylase, which converts phenylalanine to tyrosine in the presence of molecular oxygen and a catalytic amount of tetrahydrobiopterin. This enzyme plays a vital role in amino acid metabolism and neurotransmitter synthesis. Increased levels of phenylalanine and tyrosine have been associated with an increased risk of type 2 diabetes, including insulin signalling disorders through modification of β-insulin receptors and decreased glucose uptake.[70]

SNP rs2245360 may disrupt this pathway, leading to metabolic disturbances like *Impaired Fasting Glucose* (IFG), especially under beta-blocker-induced dysglycemia. The AA genotype in PAH is linked to atenolol-associated IFG, suggesting shared mechanisms for drug-induced and primary dysmetabolism.[44] The rs2245360 polymorphism in the *PAH* gene has the potential to affect the activity of the phenylalanine hydroxylase enzyme, which catalyzes the conversion of phenylalanine to tyrosine. Disruption of this pathway can lead to the accumulation of phenylalanine in the circulation. Increased phenylalanine is known to interfere with insulin signaling through phenylalanylation of lysine residues on the β subunit of the insulin receptor, resulting in decreased insulin pathway activation and reduced glucose uptake.[70]

Cooper-Dehoff et al. (2014) discovered a significant correlation between increased levels of five amino acids isoleucine, leucine, valine, tyrosine, and phenylalanine and the onset of impaired fasting glucose (IFG) following atenolol therapy. IFG is a condition where fasting glucose levels are elevated but not yet classified as diabetes. Genetic analysis showed that individuals with the AA genotype at the rs2245360 variant in the *PAH* gene had a higher incidence of IFG (41.7%) and a greater increase in fasting glucose compared to those without the AA genotype ($P<0.0001$). However, the development of IFG during β-blocker therapy is likely multifactorial. In addition to *PAH* polymorphism, other genetic factors, the patient's metabolic condition, weight gain, β2-adrenergic receptor-mediated inhibition of insulin release, and decreased insulin sensitivity may also contribute.[71,72] The interaction between *PAH* polymorphism and β-blocker therapy may represent additive or synergistic metabolic effects. *PAH* dysfunction may independently promote phenylalanine accumulation, which disrupts insulin receptor signaling.70 Therefore, individuals carrying the rs2245360 variant may be more susceptible to β-blocker-induced dysglycemia, as both genetic predisposition and pharmacological effects converge

on the glucose homeostasis pathway.

Pharmacogenomics represents a major advance in precision medicine, combining the fields of pharmacology and genomics to tailor medical treatments to an individual's unique genetic characteristics.[73] Pharmacogenomics holds the promise of optimizing drug therapy, reducing adverse drug reactions, and increasing treatment efficacy. By analyzing genetic variations that affect drug metabolism, transport and mechanisms of action, healthcare professionals can select drugs and doses that are most compatible with an individual's genetic makeup.[74,75] The use of genetic testing to personalize the treatment of hypertension has shown great potential in improving the effectiveness and safety of antihypertensive therapy, especially in countries with a high burden of hypertension such as China.[76]

Genetic testing allows clinicians to select the type of drug and dose that best suits an individual's genetic profile, thereby maximizing benefits and reducing the risk of side effects that often occur with conventional therapeutic approaches. For example, variations in the *CYP2D6* gene, which plays a role in drug metabolism, can affect the body's response to certain classes of antihypertensive drugs, such as diuretics, beta-blockers, and angiotensin receptor blockers.[77] Several major healthcare institutions in China, including Fuwai Hospital and the China-PEM (*Pharmacogenomic Examination and Management*) initiative, have utilized pharmacogenetic testing to tailor hypertension treatment in a more targeted manner. Policy support from the Chinese government, through its mid to long-term plan for chronic disease prevention, reinforces efforts to integrate genetic testing in primary healthcare.[78]

Pharmacogenetics offers the opportunity to select the right drug and dose for each hypertensive patient, given the variability of blood pressure response to drugs between individuals.[79] Although there are still challenges in its widespread application, such as the relatively small effectiveness of genetic variation and the need for multi-gene analysis, this strategy can reduce the frequency of drug switching, improve blood pressure control.[76,80] Implementation in the clinic requires the support of pharmacogenetic-based clinical decision systems as well as medical training to integrate genetic information into routine practice.[73] Precision medicine faces several challenges that hinder its full potential. One major obstacle is the availability and integration of diverse patient data, including genomics, proteomics, and Electronic Health Records (EHRs).[81] Privacy and security of data, especially genetic data, adds complexity.[82] Additionally, clinical validation and biomarker standardization are time-consuming and costly, and the lack of consistency in biomarker measurements across medical facilities further complicates the process. Since genetic variation differs between ethnicities, especially in diverse populations like Indonesia, biomarker development must account for these variations.[83] However, pharmacogenomic studies evaluating β-blocker response genes are still limited to the Southeast Asian population. Most of the available evidence comes from Western and East Asian cohorts, highlighting the urgent need for region-specific clinical studies to ensure the applicability of biomarkers in ASEAN countries. Moreover, the lack of clinician knowledge and training on genomic data and biomarkers can lead to treatment errors.[84] Precision medicine also faces resource constraints, with genomic testing being expensive, especially in less developed regions. The slow translation of research findings into clinical practice further delays its benefits.85 Regulatory and ethical issues, such as the absence of universal guidelines for genetic data use, raise concerns about privacy.[73] Finally, the high cost of genomic tests, coupled with variability in their performance, poses a significant challenge, potentially straining healthcare systems.[85]

The development of new technologies plays an important role in strengthening diagnostic capabilities and personalized medicine, enabling a more precise and adaptive approach to the unique characteristics of each patient. Several technological innovations have emerged to support precision and personalized medicine, including the use of artificial intelligence (AI), genomic platforms, and microfluidics.[86] In addition, AI contributes to accelerating drug discovery and optimizing therapeutic strategies by integrating diverse biological and clinical data. These capabilities enable healthcare systems to move toward more efficient, data-driven, and individualized medical care.[86]

The Biomedical Genome-based Science Initiative (BGSi) launched by the Ministry of Health of the Republic of Indonesia is a strategic step in encouraging the development of precision medicine based on genomic data in Indonesia. BGSi reflects Indonesia's commitment to accelerating the transformation of health technology through the integration of big data and artificial intelligence, with a focus on developing genomics-based health services.[87] In the face of challenges such as high costs, limited information technology, and low public awareness of genomics, the government has taken concrete steps through the preparation of a regulatory framework such as Kepmenkes No. HK.01.07/MENKES/1141/2022, the development of research hubs in several referral hospitals, and collaboration with various stakeholders.[87]

5. Conclusion

This review shows that interindividual variability in response to β-blockers is strongly influenced by genetic polymorphisms that affect receptor signaling, metabolic regulation, vascular function, and glucose homeostasis. Variations in *ADRB1* and *ADRB2* consistently modulate pharmacodynamic responses through altered receptor signaling efficiency, affecting heart rate control, myocardial contraction, and blood pressure reduction. Meanwhile, polymorphisms in *ACY3*, *FGD5*, *SLC4A1*, and *SLC25A31* appear to influence vascular tone and blood pressure responsiveness through neurohormonal and endothelial pathways. Additionally, metabolic-related genes such as *PRKCB*, *DPYS*, *PLEKHH2*, and *PAH* contribute to β-blocker-induced dysglycemia variability and new-onset diabetes risk, highlighting the multifactorial nature of treatment responses.

Overall, these findings suggest that β-blocker pharmacogenomics extends beyond antihypertensive efficacy to include modulation of cardiovascular function, vascular remodeling, and metabolic safety. Although some polymorphisms show promising associations, their clinical implementation requires further validation in large and ethnically diverse populations. Given the limited pharmacogenomic data from Southeast Asia, particularly Indonesia, region-specific studies are crucial to ensure the applicability of genetic biomarkers. Integrating genomic profiles into clinical decision-making could ultimately facilitate more precise β-blocker selection, optimizing therapeutic outcomes while minimizing side effects.

Conflict of Interest

The authors declare no conflicts of interest.

References

1. Liatakis I, Manta E, Tsioufis C. Hypertension and Atrial Fibrillation: Epidemiological Data, Pathogenesis, and Therapeutic Implications. American Journal of Hypertension. 2019;32(8):725–6. doi:10.1093/ajh/hpz077
2. Putri LR, Fibriana AI, Azam M. Prevalence and Risk Factors of Hypertension Among Young Adults (26-35 Years Old) in Indonesia: Analysis of Secondary Data from Riskesdas 2018. Epidemiology; 2024. Available from: http://medrxiv.org/lookup/doi/10.1101/2024.06.10.24308678 doi:10.1101/2024.06.10.24308678
3. World Health Organization. Monitoring health for the SDGs, Sustainable Development Goals. 2024. Available from: https://www.who.int/publications/i/item/9789240094703.
4. Husma SH, Setiarini A, Sartika RAD, Putri PN. Hubungan Jenis Kelamin, Usia dan Frekuensi Konsumsi Mie Instan pada Pasien Hipertensi di Wilayah Kerja Puskesmas Kemiri Muka, Kota Depok. Mal Nurse J. 2025;7(3):1392–408. doi:10.33024/mnj.v7i3.18811
5. Kasaudhan SM, Ghimire A, Sharma SK, Baral D, Jha N, Singh SB. Undiagnosed and Uncontrolled Hypertension and Access to Health Care among Residents of an Urban Area of Eastern Nepal: a Cross-sectional Study. Kathmandu Univ Med J. 2022;20(3):273–9. doi:10.3126/kumj.v20i3.53928
6. Gebremichael GB, Berhe KK, Zemichael TM. Uncontrolled hypertension and associated factors among adult hypertensive patients in Ayder comprehensive specialized hospital, Tigray, Ethiopia, 2018. BMC Cardiovasc Disord. 2019;19(1):121. doi:10.1186/s12872-019-1091-6
7. Farhadi F, Aliyari R, Ebrahimi H, Hashemi H, Emamian MH, Fotouhi A. Prevalence of uncontrolled hypertension and its associated factors in 50–74 years old Iranian adults: a population-based study. BMC Cardiovasc Disord. 2023;23(1):318. doi:10.1186/s12872-023-03357-x
8. Alhawari H, Jarrar Y, Zihlif M, Wahbeh A, Alshelleh S, Ojjoh K, et al. Variability in Response to Valsartan and Its Relationship With AGT M235T Genotype and Other Nongenetic Parameters Among a Sample of Hypertensive Individuals in Jordan: A Prospective Pilot Study. Health Science Reports. 2025;8(4):e70611. doi:10.1002/hsr2.70611
9. Derington CG, Berchie RO, Mohanty AF, Jacobs JA, Xu Y, King JB, et al. First-Line β-Blocker Use for Hypertension in the Veterans Health Administration. JAMA Netw Open. 2025;8(8):e2529026. doi:10.1001/jamanetworkopen.2025.29026
10. Magvanjav O, McDonough CW, Gong Y, McClure LA, Talbert RL, Horenstein RB, et al. Pharmacogenetic Associations of β1-Adrenergic Receptor Polymorphisms With Cardiovascular Outcomes in the SPS3 Trial (Secondary Prevention of Small Subcortical Strokes). Stroke. 2017;48(5):1337–43. doi:10.1161/STROKEAHA.116.015936
11. Farzam K, Jan A. Beta Blockers. In. Treasure Island: StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532906/.
12. Park JJ, Park H, Cho H, Lee H, Kim KH, Yoo B, et al. β-Blockers and 1-Year Postdischarge Mortality for Heart Failure and Reduced Ejection Fraction and Slow Discharge Heart Rate. JAHA. 2019;8(4):e011121. doi:10.1161/JAHA.118.011121
13. Robiou-du-Pont S, Anand SS, Morrison KM, McDonald SD, Atkinson SA, Teo KK, et al. Parental and offspring contribution of genetic markers of adult blood pressure in early life: The FAMILY study. Dubé MP, editor. PLoS ONE. 2017;12(10):e0186218. doi:10.1371/journal.pone.0186218
14. Warren HR, Evangelou E, Cabrera CP, Gao H, Ren M, Mifsud B, et al. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. Nat Genet. 2017;49(3):403–15. doi:10.1038/ng.3768
15. the Million Veteran Program, Evangelou E, Warren HR, Mosen-Ansorena D, Mifsud B, Pazoki R, et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. Nat Genet.

2018;50(10):1412–25. doi:10.1038/s41588-018-0205-x
16. Pinheiro DS, Santos RS, Jardim PCBV, Silva EG, Reis AAS, Pedrino GR, et al. The combination of ACE I/D and ACE2 G8790A polymorphisms revels susceptibility to hypertension: A genetic association study in Brazilian patients. Ciccacci C, editor. PLOS ONE. 2019;14(8):e0221248.
17. Gong Y, Wang Z, Beitelshees AL, McDonough CW, Langaee TY, Hall K, et al. Pharmacogenomic Genome-Wide Meta-Analysis of Blood Pressure Response to β-Blockers in Hypertensive African Americans. Hypertension. 2016;67(3):556–63.
18. Razaq A, Khan A, Shah ST, Ullah S. Association of insertion /deletion polymorphism of ace gene with essential hypertension in patients of Khyber Pakhtunkhwa. Pakistan Journal of Medical Sciences. 2023;40(3).
19. Devyatkin VA, Redina OE, Muraleva NA, Kolosova NG. Single-Nucleotide Polymorphisms (SNPs) Both Associated with Hypertension and Contributing to Accelerated-Senescence Traits in OXYS Rats. International Journal of Molecular Sciences. 2020;21(10):3542.
20. Dawed AY, Mari A, Brown A, McDonald TJ, Li L, Wang S, et al. Pharmacogenomics of GLP-1 receptor agonists: a genome-wide analysis of observational data and large randomised controlled trials. The Lancet Diabetes & Endocrinology. 2023;11(1):33–41. doi:10.1016/S2213-8587(22)00340-0
21. Greden JF, Parikh SV, Rothschild AJ, Thase ME, Dunlop BW, DeBattista C, et al. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study. Journal of Psychiatric Research. 2019;111:59–67. doi:10.1016/j.jpsychires.2019.01.003
22. Lou JS, Su M, Wang J, Do HN, Miao Y, Huang XY. Distinct binding conformations of epinephrine with α- and β-adrenergic receptors. Exp Mol Med. 2024;56(9):1952–66. doi:10.1038/s12276-024-01296-x
23. Do Vale GT, Ceron CS, Gonzaga NA, Simplicio JA, Padovan JC. Three Generations of β-blockers: History, Class Differences and Clinical Applicability. Current Hypertension Reviews. 2019;15(1):22–31.
24. Park K, Park TH. Comparative effects of nebivolol and carvedilol on left ventricular diastolic function in older patients with heart failure and preserved ejection fraction. International Journal of Cardiology Cardiovascular Risk and Prevention. 2023;18:200201. doi:10.1016/j.ijcrp.2023.200201
25. Chan You S, Krumholz HM, Suchard MA, Schuemie MJ, Hripcsak G, Chen R, et al. Comprehensive Comparative Effectiveness and Safety of First-Line β-Blocker Monotherapy in Hypertensive Patients: A Large-Scale Multicenter Observational Study. Hypertension. 2021;77(5):1528–38. doi:10.1161/HYPERTENSIONAHA.120.16402
26. Gao X, Liu M, Xu J, Li L, Chen M, Lang X, et al. Impact of in-hospital oral beta-blockers initiation on long-term outcomes in ST-elevation myocardial infarction patients with cardiogenic shock. Front Med. 2025;12:1666977. doi:10.3389/fmed.2025.1666977
27. Shahin MH, Conrado DJ, Gonzalez D, Gong Y, Lobmeyer MT, Beitelshees AL, et al. Genome-Wide Association Approach Identified Novel Genetic Predictors of Heart Rate Response to β-Blockers. JAHA. 2018;7(5):e006463. doi:10.1161/JAHA.117.006463
28. Yang HQ, Wang LP, Gong YY, Fan XX, Zhu SY, Wang XT, et al. β2 -Adrenergic Stimulation Compartmentalizes β1 Signaling Into Nanoscale Local Domains by Targeting the C-Terminus of β1 -Adrenoceptors. Circulation Research. 2019;124(9):1350–9. doi:10.1161/CIRCRESAHA.118.314322
29. Shannon TR, Bare DJ, Van Dijk S, Raofi S, Huynh TNM, Xiang YK, et al. Subcellular Propagation of Cardiomyocyte β-Adrenergic Activation of Calcium Uptake Involves Internal β-Receptors and AKAP7. Function. 2022;3(3):zqac020. doi:10.1093/function/zqac020
30. Diaconu C, Marcu D, Bratu O, Stanescu AM, Gheorghe G, Hlescu A, et al. Beta-blockers in Cardiovascular Therapy: A Review. JMMS. 2019;6(2):216–23. doi:10.22543/7674.62.P216223
31. Xu W, Li J, Ju J, Liu M, Wang W, Cheng M, et al. The beta1-adrenergic receptor in the heart. Cell Death Discov. 2025;12(1):46. doi:10.1038/s41420-025-02907-w
32. Humphries S, Mars K, Hofmann R, Held C, Olsson EMG. Randomized evaluation of routine beta-blocker therapy after myocardial infarction quality of life (RQoL): design and rationale of a multicentre, prospective, randomized, open, blinded endpoint study. Banach M, editor. European Heart Journal Open. 2023;3(3):oead036. doi:10.1093/ehjopen/oead036
33. Dungan K, Merrill J, Long C, Binkley P. Effect of beta blocker use and type on hypoglycemia risk among hospitalized insulin requiring patients. Cardiovasc Diabetol. 2019;18(1):163. doi:10.1186/s12933-019-0967-1
34. Gill D, Georgakis MK, Koskeridis F, Jiang L, Feng Q, Wei WQ, et al. Use of Genetic Variants Related to Antihypertensive Drugs to Inform on Efficacy and Side Effects. Circulation. 2019;140(4):270–9.
35. Castaño-Amores C, Antúnez-Rodríguez A, Pozo-Agundo A, García-Rodríguez S, Martínez-González LJ, Dávila-Fajardo CL. Genetic polymorphisms in *ADRB1*, *ADRB2* and CYP2D6 genes and response to beta-blockers in patients with acute coronary syndrome. Biomedicine & Pharmacotherapy. 2023;169:115869.
36. Rimpelä JM, Kontula KK, Fyhrquist F, Donner KM, Tuiskula AM, Sarin AP, et al. Replicated Evidence for Aminoacylase 3 and Nephrin Gene Variations to Predict Antihypertensive Drug Responses. Pharmacogenomics. 2017;18(5):445–58.
37. Chang S, Gong Y, McDonough C, Langaee T, Nasiri Kenari N, Beitelshees A, et al. Melatonin Pathway and Atenolol-Related Glucose Dysregulation: Is There a Correlation? Clinical and Translational Science. 2016;9(2):114–22.
38. Van Driest SL, Sleeper LA, Gelb BD, Morris SA, Dietz HC, Forbus GA, et al. Variants in *ADRB1* and CYP2C9: Association with Response to Atenolol and Losartan in Marfan Syndrome. The Journal of Pediatrics. 2020;222:213–20.
39. Shahin MH, Rouby NE, Conrado DJ, Gonzalez D, Gong Y, Lobmeyer MT, et al. β2 -Adrenergic Receptor

Gene Affects the Heart Rate Response of β-Blockers: Evidence From 3 Clinical Studies. J Clin Pharmacol. 2019;59(11):1462–70.
40. Singh S, El Rouby N, McDonough CW, Gong Y, Bailey KR, Boerwinkle E, et al. Genomic Association Analysis Reveals Variants Associated With Blood Pressure Response to Beta-Blockers in European Americans. Clinical and Translational Science. 2019;12(5):497–504.
41. Peller M, Ozierański K, Balsam P, Grabowski M, Filipiak KJ, Opolski G. Influence of beta-blockers on endothelial function: A meta-analysis of randomized controlled trials. Cardiology Journal. 2015;22(6):708–16. Available from: https://journals.viamedica.pl/cardiology_journal/article/view/41777
42. Chang SW, McDonough CW, Gong Y, Johnson TA, Tsunoda T, Gamazon ER, et al. Genome-wide association study identifies pharmacogenomic loci linked with specific antihypertensive drug treatment and new-onset diabetes. The Pharmacogenomics Journal. 2018;18(1):106–12.
43. De Oliveira FA, Shahin MH, Gong Y, McDonough CW, Beitelshees AL, Gums JG, et al. Novel plasma biomarker of atenolol-induced hyperglycemia identified through a metabolomics-genomics integrative approach. Metabolomics. 2016;12(8):129. Available from: http://link.springer.com/10.1007/s11306-016-1076-8
44. Cooper-DeHoff RM, Hou W, Weng L, Baillie RA, Beitelshees AL, Gong Y, et al. Is a Diabetes Mellitus–Linked Amino Acid Signature Associated With β-Blocker–Induced Impaired Fasting Glucose? Circulation: Cardiovascular Genetics. 2014;7(2):199–205.
45. Raimoglou D. Structural and Functional Impact of Adrenoceptor Beta-1 Gene Polymorphism in Patients with Hypertrophic Cardiomyopathy and Response to Beta-Blocker Therapy. Anatol J Cardiol. 2024;150–7. doi:10.14744/AnatolJCardiol.2023.3898
46. Wu D, Li G, Deng M, Song W, Huang X, Guo X, et al. Associations between *ADRB1* and CYP2D6 gene polymorphisms and the response to β-blocker therapy in hypertension. J Int Med Res. 2015;43(3):424–34. doi:10.1177/0300060514563151
47. Dalangin R, Kim A, Campbell RE. The Role of Amino Acids in Neurotransmission and Fluorescent Tools for Their Detection. International Journal of Molecular Sciences. 2020;21(17):6197.
48. Hiltunen TP, Donner KM, Sarin AP, Saarela J, Ripatti S, Chapman AB, et al. Pharmacogenomics of hypertension: a genome-wide, placebo-controlled cross-over study, using four classes of antihypertensive drugs. JAHA. 2015;4(1):e001778. doi:10.1161/JAHA.115.001778
49. Si D, Wang J, Xu Y, Chen X, Zhang M, Zhou H. Association of Common Polymorphisms in β1-adrenergic Receptor With Antihypertensive Response to Carvedilol: Journal of Cardiovascular Pharmacology. 2014;64(4):306–9.
50. Muslimova E, Rebrova T, Kondratieva D, Korepanov V, Sonduev E, Kozlov B, et al. Expression of the β1-adrenergic receptor (*ADRB1*) gene in the myocardium and β-adrenergic reactivity of the body in patients with a history of myocardium infraction. Gene. 2022;844:146820.
51. Myagmar BE, Flynn JM, Cowley PM, Swigart PM, Montgomery MD, Thai K, et al. Adrenergic Receptors in Individual Ventricular Myocytes: The Beta-1 and Alpha-1B Are in All Cells, the Alpha-1A Is in a Subpopulation, and the Beta-2 and Beta-3 Are Mostly Absent. Circulation Research. 2017;120(7):1103–15.
52. McCrink KA, Brill A, Jafferjee M, Valero TR, Marrero C, Rodriguez MM, et al. β1 -Adrenoceptor Arg389Gly Polymorphism Confers Differential β-Arrestin-Binding Tropism in Cardiac Myocytes. Pharmacogenomics. 2016;17(15):1611–20. doi:10.2217/pgs-2016-0094
53. Moric-Janiszewska E, Smolik S, Szydłowski L, Kapral M. Associations between Selected *ADRB1* and CYP2D6 Gene Polymorphisms in Children with Ventricular and Supraventricular Arrhythmias. Medicina. 2023;59(12):2057.
54. Atici A, Rasih-Sonsoz M, Ali-Barman H, Durmaz E, Demirkiran A, Gulsen K, et al. The Role of Beta-1 Receptor Gene Polymorphism in Beta-Blocker Therapy for Vasovagal Syncope. RIC. 2020;72(5):3938. doi:10.24875/RIC.20003319
55. Pranckevicius NA, Scott AL, Rourke AJ, Saleem R, Wearing OH, Scott GR. Catecholamine synthesis and secretion by adrenal chromaffin cells are reduced in deer mice native to high altitude. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2025;328(3):R274–86. doi:10.1152/ajpregu.00194.2024
56. Liu Y, Wang Y, Zhou M, Zhang L, Pang Y, Wang C, et al. Metabolism and secretion mechanism of catecholamine syndrome and related treatment strategies. J Xiangya Med. 2020;5:39–39. doi:10.21037/jxym-20-88
57. Würtz P, Havulinna AS, Soininen P, Tynkkynen T, Prieto-Merino D, Tillin T, et al. Metabolite Profiling and Cardiovascular Event Risk: A Prospective Study of 3 Population-Based Cohorts. Circulation. 2015;131(9):774–85.
58. Chen H, Luo H, Zhou J, Yu M, Qing T, Wang Y, et al. Polymorphisms in genes related to inflammation and endothelial function are associated with ischemic stroke and other vascular events in populations at high risk of stroke. J Cent Nerv Syst Dis. 2025;17:11795735241312660. doi:10.1177/11795735241312660
59. Farhan MA, Azad AK, Touret N, Murray AG. FGD5 Regulates VEGF Receptor-2 Coupling to PI3 Kinase and Receptor Recycling. Arteriosclerosis, Thrombosis, and Vascular Biology. 2017;37(12):2301–10.
60. Ta N, Liu M, Wang Y, Zeng F, Nie F, Shang M, et al. Association of polymorphisms in endothelial dysfunction-related genes with susceptibility to essential hypertension in elderly Han population in Liaoning province, China. Rev Cardiovasc Med. 2021;22(3):895. doi:10.31083/j.rcm2203096
61. Li B, Zhang Q, Zhang H, Wang C, Xiu R. Effects of nebivolol versus other antihypertensive drugs on the endothelial dysfunction in patients with essential hypertension. Bioscience Reports. 2020;40(5):BSR20200436. doi:10.1042/BSR20200436
62. Majidinia M, Rasmi Y, Khadem Ansari MH, Seyed-Mohammadzad M, Saboory E, Shirpoor A. Metoprolol Improves Endothelial Function in Patients with Cardiac Syndrome X. Iran J Pharm Res. 2016;15(3):561–6.

PubMed PMID: 27980592; PubMed Central PMCID: PMC5149044.
63. Bertocchio JP, Genetet S, Da Costa L, Walsh SB, Knebelmann B, Galimand J, et al. Red Blood Cell AE1/Band 3 Transports in Dominant Distal Renal Tubular Acidosis Patients. Kidney International Reports. 2020;5(3):348–57. doi:10.1016/j.ekir.2019.12.020
64. Zhou Y, Qiu L, Xiao Q, Wang Y, Meng X, Xu R, et al. Obesity and diabetes related plasma amino acid alterations. Clinical Biochemistry. 2013;46(15):1447–52.
65. Love KM, Jahn LA, Hartline LM, Patrie JT, Barrett EJ, Liu Z. Insulin-mediated muscle microvascular perfusion and its phenotypic predictors in humans. Sci Rep. 2021;11(1):11433. doi:10.1038/s41598-021-90935-8
66. Xia AY, Zhu H, Zhao ZJ, Liu HY, Wang PH, Ji LD, et al. Molecular Mechanisms of the Melatonin Receptor Pathway Linking Circadian Rhythm to Type 2 Diabetes Mellitus. Nutrients. 2023;15(6):1406.
67. Kanehisa M, Goto S, Sato Y, Kawashima M, Furumichi M, Tanabe M. Data, information, knowledge and principle: back to metabolism in KEGG. Nucleic Acids Research. 2014;42(1):199–205.
68. Wang J, Casimiro-Garcia A, Johnson BG, Duffen J, Cain M, Savary L, et al. A protein kinase C α and β inhibitor blunts hyperphagia to halt renal function decline and reduces adiposity in a rat model of obesity-driven type 2 diabetes. Sci Rep. 2023;13(1):16919. doi:10.1038/s41598-023-43759-7
69. Luo JQ, Ren H, Chen MY, Zhao Q, Yang N, Liu Q, et al. Hydrochlorothiazide-induced glucose metabolism disorder is mediated by the gut microbiota via LPS-TLR4-related macrophage polarization. iScience. 2023;26(7):107130. doi:10.1016/j.isci.2023.107130
70. Zhou Q, Sun WW, Chen JC, Zhang HL, Liu J, Lin Y, et al. Phenylalanine impairs insulin signaling and inhibits glucose uptake through modification of IRβ. Nat Commun. 2022;13(1):4291. doi:10.1038/s41467-022-32000-0
71. Jain AB, Lai V. Medication-Induced Hyperglycemia and Diabetes Mellitus: A Review of Current Literature and Practical Management Strategies. Diabetes Ther. 2024;15(9):2001–25. doi:10.1007/s13300-024-01628-0
72. Rokamp KZ, Staalsø JM, Zaar M, Rasmussen P, Petersen LG, Nielsen RV, et al. The Gly16 Allele of the G16R Single Nucleotide Polymorphism in the β2-Adrenergic Receptor Gene Augments the Glycemic Response to Adrenaline in Humans. Front Physiol. 2017;8:661. doi:10.3389/fphys.2017.00661
73. Tremmel R, Schreeck F, Jaeger S, Schricker S, Schaeffeler E, Igel S, et al. Clinical Implementation of Pharmacogenomics and Drug–Drug Interaction Screening in a German Academic Teaching Hospital and Outpatient Follow-Up. Clin Pharma and Therapeutics. 2026;119(1):241–54. doi:10.1002/cpt.70083
74. Swen JJ, Van Der Wouden CH, Manson LE, Abdullah-Koolmees H, Blagec K, Blagus T, et al. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. The Lancet. 2023;401(10374):347–56. doi:10.1016/S0140-6736(22)01841-4
75. Chen C, Lun Y, Yu J, Zhao X, Su S, Zhao M, et al. Effects of pharmacogenomics-guided treatment on medication adherence and the antidepressant switching rate in major depressive disorder. Front Pharmacol. 2024;15:1501381. doi:10.3389/fphar.2024.1501381
76. Xiao ZL, Yang M, Chen XB, Xie XM, Chen MF. Personalized antihypertensive treatment guided by pharmacogenomics in China. Cardiovasc Diagn Ther. 2022;12(5):635–45. doi:10.21037/cdt-22-154
77. Chan SW, Chu TTW, Ho CS, Kong APS, Tomlinson B, Zeng W. Influence of CYP2D6 and CYP3A5 Polymorphisms on the Pharmacokinetics and Pharmacodynamics of Bisoprolol in Hypertensive Chinese Patients. Front Med. 2021;8:683498. doi:10.3389/fmed.2021.683498
78. Liu Z, Cheng Z, Ye S, Zhou L, Zhou Z. Catalytic Ability Improvement of Phenylalanine Hydroxylase from Chromobacterium violaceum by N-Terminal Truncation and Proline Introduction. Journal of Microbiology and Biotechnology. 2019;29(9):1375–82.
79. Jan A, Alanzi A, Mothana R, Kaimori JY, Ali S, Muhammad T, et al. Pharmacogenomic Study of Selected Genes Affecting Amlodipine Blood Pressure Response in Patients with Hypertension. PGPM. 2024;Volume 17:473–86. doi:10.2147/PGPM.S481068
80. Wang A, Mbikyo MB, Zhang J, Cui N, Li Z, et al. Treatment for Resistant Hypertension Under the Guidance of Pharmacogenomics: A Randomised Controlled Open-Label Trial. J Coll Physicians Surg Pak. 2024;34(04):383–9. doi:10.29271/jcpsp.2024.04.383
81. Weinshilboum RM, Wang L. Pharmacogenomics: Precision Medicine and Drug Response. Mayo Clinic Proceedings. 2017;92(11):1711–22. doi:10.1016/j.mayocp.2017.09.001
82. Briguglio W, Moghaddam P, Yousef WA, Traore I, Mamun M. Machine Learning in Precision Medicine to Preserve Privacy via Encryption. Pattern Recognition Letters. 2021;151:148–54. doi:10.1016/j.patrec.2021.07.004
83. Sharma S, Mariño-Ramírez L, Jordan IK. Race, Ethnicity, and Pharmacogenomic Variation in the United States and the United Kingdom. Pharmaceutics. 2023;15(7):1923. doi:10.3390/pharmaceutics15071923
84. Panconesi D, Murtough S, Cotic M, Khani NS, Varney L, Richards-Brown M, et al. Pharmacogenomics to optimise psychotropic prescribing: a survey of mental health professionals' perceptions, knowledge, and educational needs. Pharmacogenomics J. 2026;26(1):2. doi:10.1038/s41397-025-00394-x
85. Ayati N, Afzali M, Hasanzad M, Kebriaeezadeh A, Rajabzadeh A, Nikfar S. Pharmacogenomics Implementation and Hurdles to Overcome; In the Context of a Developing Country. IJPR. 2021;20(4). doi:10.22037/ijpr.2021.114899.15091
86. Ho D, Quake SR, McCabe ERB, Chng WJ, Chow EK, Ding X, et al. Enabling Technologies for Personalized and Precision Medicine. Trends in Biotechnology. 2020;38(5):497–518. doi:10.1016/j.tibtech.2019.12.021
87. Kamelia T, Putri NAR. Perkembangan PRECISION Medicine Di Indonesia. Indonesia Journal Chest. 2023;10(1):1–12.