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Pharmacogenomics in Cardiovascular Pharmacology: Toward Precision Medicine in Hypertension and Heart Failure

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Abstract:

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, posing a persistent challenge to global health systems. Despite significant advancements in drug discovery and therapeutic interventions, interindividual variability in drug response continues to limit treatment efficacy and safety. Pharmacogenomics, the science of understanding how genetic variations affect drug response, has emerged as a crucial tool in addressing this variability and advancing personalized cardiovascular therapy. In conditions such as hypertension and heart failure, genetic polymorphisms in drug-metabolizing enzymes, transporters, and molecular targets have been shown to influence therapeutic outcomes and adverse event profiles. Variants in genes such as ADRB1, ADRB2, ACE, AGTR1, and SLC12A3 modulate patient responses to widely used cardiovascular drugs including β-blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), and diuretics. Understanding these gene–drug interactions enables clinicians to tailor pharmacological strategies to an individual's genetic makeup, improving efficacy while minimizing toxicity. Furthermore, the integration of multi-omics technologies—including transcriptomics, metabolomics, and proteomics—alongside polygenic risk scoring and machine learning–based models is transforming cardiovascular pharmacogenomics from a single-gene focus to a systems-level understanding. These integrative approaches hold the potential to predict not only therapeutic responses but also disease progression and adverse drug reactions in real time. Ultimately, pharmacogenomics is propelling cardiovascular medicine toward a precision-driven era, where treatments are informed by an individual's unique genetic and molecular profile rather than population averages. This paradigm shift promises more accurate, effective, and safer interventions in the management of CVDs.

Keywords: Pharmacogenomics, Cardiovascular Diseases, Hypertension, Heart Failure, β-blockers, ACE Inhibitors, ARBs, Precision Medicine, Genetic Polymorphisms, Multi-omics Integration

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1. Introduction

Despite decades of groundbreaking research, cardiovascular disease management continues to be one of medicine's most complex balancing acts. It's a scenario that plays out in hospitals every day—two patients are prescribed the same antihypertensive medication, yet their outcomes are worlds apart. One patient's blood pressure normalizes effortlessly, while the other struggles with persistent hypertension or debilitating side effects. This stark difference isn't just bad luck—it's biology. Beneath these contrasting responses lies the intricate web of human genetic diversity, which shapes how each body reacts to drugs [1-2].

Pharmacogenomics emerges as the key to decoding this mystery. By examining how genetic variations—particularly single nucleotide polymorphisms (SNPs)—influence drug metabolism, efficacy, and toxicity, pharmacogenomics bridges the frustrating gap between conventional "one-size-fits-all" prescriptions and individualized treatment. It moves medicine beyond guesswork, offering a molecular explanation for why identical therapies yield unpredictable results [3].

In the broader landscape of precision medicine, pharmacogenomics represents one of the most transformative frontiers. Precision medicine seeks to customize healthcare by integrating an individual's genetic, environmental, and lifestyle data into clinical decision-making. Within cardiovascular pharmacology, this personalization is taken a step further—by identifying genetic markers that predict how a patient will respond to specific drugs, clinicians can fine-tune therapy for maximum benefit and minimal risk [4]. The mission is ambitious yet clear: to deliver the right drug, at the right dose, to the right patient, at precisely the right time. This paradigm shift not only enhances treatment efficacy but also redefines patient safety and therapeutic predictability in cardiovascular care.

2. Pharmacogenomics and Hypertension

Hypertension, often dubbed the "silent killer," remains one of the most prevalent and preventable cardiovascular conditions worldwide. While lifestyle factors such as diet, stress, and physical activity undoubtedly play major roles in its onset and progression, genetics often dictate how well an individual responds to antihypertensive therapy. Pharmacogenomics—by decoding these genetic differences—provides a roadmap for optimizing blood pressure control and minimizing adverse effects. Understanding how gene variants influence drug response enables clinicians to move beyond trial-and-error prescribing and instead adopt a more predictive, targeted approach to therapy [5-6].

2.1. Overview of Antihypertensive Drug Classes

The pharmacological management of hypertension primarily revolves around four major classes of drugs: β-blockers, calcium channel blockers (CCBs), renin–angiotensin system (RAS) inhibitors, and diuretics. Each of these classes works through distinct mechanisms—β-blockers slow heart rate and reduce cardiac output, CCBs relax vascular smooth muscles, RAS

inhibitors target hormonal control of vascular tone, and diuretics decrease blood volume by promoting sodium and water excretion [7-8]. However, despite their proven efficacy, not all patients experience equal benefit. Over the past decade, numerous studies have identified genetic polymorphisms that influence both the pharmacokinetics (drug absorption, metabolism, and excretion) and pharmacodynamics (drug–receptor interaction and response) of these medications. This growing body of evidence underscores the importance of integrating genetic insights into hypertension treatment strategies [9].

2.2. β-Adrenergic Receptor Polymorphisms

β-blockers, such as metoprolol and atenolol, remain a cornerstone therapy in hypertension management, particularly for patients with comorbid conditions like arrhythmia or post-myocardial infarction. These drugs exert their effects primarily through β1-adrenergic receptors encoded by the ADRB1 gene [10]. Two key genetic variants—Ser49Gly and Arg389Gly—have been shown to significantly alter therapeutic outcomes. Carriers of the Arg389 allele demonstrate enhanced receptor coupling and superior responsiveness to β-blockers, resulting in greater blood pressure reduction and improved heart rate control. In contrast, individuals carrying the Gly389 variant often experience a blunted therapeutic response [11].

Additionally, polymorphisms in the ADRB2 gene, particularly Gly16Arg and Gln27Glu, influence β2-receptor–mediated vasodilation and can further modify drug efficacy. For instance, certain populations with the Arg16 variant may show diminished responsiveness to β-blockers, highlighting the need for population-specific pharmacogenomic profiling. These findings collectively emphasize how subtle genetic variations can dictate the success or failure of commonly prescribed cardiovascular drugs [12].

2.3. Renin–Angiotensin System (RAS) Gene Variants

The renin–angiotensin system plays a pivotal role in blood pressure regulation, and agents targeting this pathway—such as ACE inhibitors and angiotensin receptor blockers (ARBs)—are fundamental to modern hypertension therapy [13]. Among the most extensively studied genetic markers in this system is the ACE I/D polymorphism, which involves an insertion (I) or deletion (D) in intron 16 of the ACE gene. The D allele is associated with higher circulating and tissue ACE levels, leading to increased angiotensin II formation. Clinically, individuals carrying the D allele often exhibit a more pronounced blood pressure reduction when treated with ACE inhibitors compared to I allele carriers [14].

Another key variant is the AGTR1 (A1166C) polymorphism, which affects the angiotensin II type 1 receptor's sensitivity and binding affinity. The C allele has been linked to reduced responsiveness to ARBs like losartan, potentially necessitating dosage adjustments or alternative therapy [15]. Genetic screening for these variants provides valuable insights that can

guide clinicians in selecting the most appropriate RAS-targeting agents for each patient, thereby improving therapeutic precision.

2.4. Diuretic Response and SLC12A3 Variants

Diuretics, particularly thiazide-type agents like hydrochlorothiazide, are among the most widely used antihypertensive medications, especially in first-line therapy. These drugs act by inhibiting the sodium-chloride cotransporter (NCC) in the distal convoluted tubule, a process governed by the SLC12A3 gene. Certain polymorphisms in SLC12A3 can alter NCC expression or function, leading to variability in sodium reabsorption and thus modifying the overall antihypertensive response [16].

Furthermore, variations in KCNJ1, the gene encoding the renal potassium channel ROMK, also influence patient outcomes. These variants can predispose individuals to electrolyte imbalances—particularly hypokalemia—during diuretic therapy. As pharmacogenomic testing becomes more accessible, identifying such genetic markers before initiating diuretics could help personalize dosage, monitor adverse effects more effectively, and ultimately improve therapeutic outcomes [17].

In essence, the pharmacogenomics of hypertension provides a molecular foundation for personalizing treatment strategies. By integrating genetic testing into routine clinical practice, healthcare providers can transition from generalized hypertension management toward an era of precision cardiovascular therapy—where treatment decisions are guided not by averages, but by individual genetic blueprints.

3. Pharmacogenomics in Heart Failure

Heart failure (HF) is a multifactorial condition marked by impaired cardiac output and systemic congestion, resulting from a complex interplay of genetic susceptibility, neurohormonal imbalance, and hemodynamic stress. Despite major therapeutic advances, patient outcomes in HF vary widely—some individuals experience dramatic recovery of cardiac function, while others show minimal improvement or adverse reactions to standard therapy [18-19]. This variability underscores the role of genetics in shaping drug efficacy and tolerance. Pharmacogenomics is rapidly illuminating how inherited gene variants influence the response to cornerstone HF medications such as β-blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), and even novel therapies like sacubitril/valsartan. By integrating genetic profiling into heart failure management, clinicians can optimize treatment selection, dosage, and timing to maximize therapeutic benefit and reduce the risk of complications [20-21].

3.1. β-Blockers and ADRB1/ADRB2 Variants

β-blockers are among the most essential drugs in chronic heart failure management, improving survival by counteracting sympathetic overactivation and protecting the myocardium from catecholamine-induced damage. However, not all patients experience the same degree of

benefit, and pharmacogenomics provides crucial insight into why [22]. Variants in the ADRB1 gene, particularly Arg389Gly, have been consistently linked to differential β-blocker response. Individuals carrying the Arg389 allele exhibit enhanced receptor coupling and superior response to β-blocker therapy, reflected in greater improvements in left ventricular ejection fraction (LVEF) and overall cardiac remodeling when treated with agents like metoprolol and bisoprolol. Conversely, Gly389 carriers tend to have a weaker receptor response, often requiring dosage adjustments or alternative therapy to achieve similar clinical outcomes [23].

The ADRB2 gene also plays a significant role, especially through the Gln27Glu polymorphism. Studies have shown that carriers of the Glu27 variant exhibit a more pronounced response to carvedilol, possibly due to improved vasodilator capacity and receptor sensitivity. These findings suggest that genotyping β-adrenergic receptor variants could help clinicians personalize β-blocker therapy, ensuring that patients receive not only the right drug but also the most effective dose based on their genetic makeup (Figure 1) [24].

3.2. ACE Inhibitors and ACE I/D Polymorphism

ACE inhibitors remain a foundational therapy in heart failure due to their ability to suppress the renin–angiotensin–aldosterone system (RAAS), reducing afterload and preventing adverse cardiac remodeling. Yet, response variability among patients has long puzzled clinicians. The ACE I/D polymorphism, which involves the insertion (I) or deletion (D) of a 287-base pair sequence in intron 16 of the ACE gene, offers part of the explanation. The D allele is associated with elevated circulating and tissue ACE levels, resulting in increased angiotensin II activity. Paradoxically, D allele carriers often derive greater benefit from ACE inhibitors, showing improved ventricular remodeling, fewer hospitalizations, and enhanced long-term survival compared to I allele carriers [25-26].

This relationship highlights a critical pharmacogenomic principle—higher baseline enzyme activity (due to genetic variation) can sometimes amplify a drug's therapeutic effect, particularly when the drug's mechanism directly targets that pathway. As precision cardiology advances, ACE genotyping could become a valuable clinical tool for predicting and optimizing ACE inhibitor responsiveness in HF patients [27].

3.3. Novel Targets: Natriuretic Peptides and NEP Inhibition

The advent of sacubitril/valsartan, a first-in-class angiotensin receptor–neprilysin inhibitor (ARNI), has redefined the management of heart failure with reduced ejection fraction (HFrEF). This combination therapy enhances the beneficial effects of natriuretic peptides—vasodilation, natriuresis, and inhibition of cardiac fibrosis—while simultaneously blocking the harmful effects of angiotensin II. However, patient responses to ARNIs also vary, and emerging research suggests a genetic basis for these differences [28].

Variants in the NPR3 gene, which encodes the natriuretic peptide clearance receptor (NPR-C), and MME, which encodes the enzyme neprilysin (NEP), may influence circulating levels of

natriuretic peptides and modulate the therapeutic response to sacubitril/valsartan. For instance, specific MME polymorphisms can alter NEP expression or activity, potentially impacting how effectively sacubitril inhibits peptide degradation. Similarly, certain NPR3 variants may affect peptide clearance, leading to interindividual differences in hemodynamic improvement and symptom relief [29].

As pharmacogenomic studies on ARNIs expand, these insights are expected to play a pivotal role in guiding future precision heart failure therapy. By integrating genetic data into treatment planning, clinicians can more accurately predict who will benefit most from advanced therapies like sacubitril/valsartan—marking another step toward truly individualized cardiovascular medicine (Table 1).

4. Emerging Omics and Polygenic Approaches

While single-gene pharmacogenomic studies have illuminated key genetic contributors to cardiovascular drug response, the next evolution of precision medicine lies in *multi-omics integration*. The human body operates through interconnected biological networks, and focusing on one gene at a time often misses the broader picture. Emerging approaches that combine genomics, transcriptomics, proteomics, and metabolomics offer a more complete view of the mechanisms governing both therapeutic efficacy and toxicity [30-31]. Together, these layers form a dynamic "pharmacophenome"—a comprehensive molecular fingerprint that links an individual's biological state to their drug response profile.

A particularly exciting advancement is the development of polygenic risk scores (PRS), which aggregate the effects of multiple genetic variants to predict disease risk and treatment outcomes. In cardiovascular medicine, PRS models are already being used to identify individuals at heightened genetic risk for hypertension, heart failure, and adverse drug reactions. For example, combining SNP data from β-adrenergic, ACE, and sodium channel genes may predict not only which patients will respond best to β-blockers or ACE inhibitors but also who may be predisposed to side effects such as hypotension or electrolyte imbalance [32-33].

Adding to this, machine learning and AI-driven analytics are becoming game changers. These models can process enormous datasets from pharmacogenomic studies and electronic health records (EHRs) to detect hidden patterns and make predictive recommendations in real time. Imagine an algorithm that automatically adjusts a patient's antihypertensive dosage based on their genomic profile, blood pressure trends, and comorbidities—that's no longer science fiction but a rapidly approaching reality [34-35]. In both hypertension and heart failure management, such integrative AI models could redefine clinical decision-making, transforming therapy from empirical to truly data-driven precision care.

5. Challenges and Future Perspectives

Despite its promise, the clinical implementation of pharmacogenomics faces significant hurdles. The first challenge is *clinical validation*—translating genomic findings from controlled studies into consistent, real-world clinical outcomes. Many gene–drug associations remain population-specific or insufficiently replicated across diverse cohorts, making it difficult to establish universal guidelines [36]. The second major barrier is *accessibility*. Pharmacogenomic testing remains expensive in many regions and is often unavailable outside specialized centers. This limits its inclusion in standard treatment protocols, particularly in resource-limited healthcare systems.

Another critical issue is the lack of standardized frameworks for integrating pharmacogenomic data into routine medical practice. While some countries have begun to incorporate pharmacogenetic information into drug labeling, global harmonization is still lacking. Moreover, ethnic and regional genetic variability further complicates clinical translation. Variants that predict strong drug responses in one population may have little to no relevance in another. Thus, large-scale, multi-ethnic studies are essential to ensure equitable and accurate genomic medicine [37-38].

Nevertheless, the future looks bright. With rapid advancements in genomic sequencing, costs are dropping dramatically, and technologies like AI-based dosing algorithms, pharmacogenetic smart cards, and EHR-integrated genomic alerts are emerging as practical tools for clinicians. These systems could automatically flag potential gene–drug interactions or suggest optimized therapy options, bringing precision pharmacology directly to the bedside. As global consortia and public–private collaborations expand, the integration of pharmacogenomics into cardiovascular medicine is moving from aspiration to implementation [39-40].

6. Conclusion

Pharmacogenomics is redefining cardiovascular pharmacology, shifting the paradigm from reactive disease management to *predictive and personalized care*. In conditions like hypertension and heart failure, understanding genetic variations in β-adrenergic receptors, ACE, and RAS pathways has already begun to guide individualized therapy—enhancing efficacy, minimizing toxicity, and improving patient outcomes. What once seemed futuristic is now within clinical reach.

As multi-omics technologies mature and AI-powered predictive models become mainstream, the once-distant dream of tailoring cardiovascular therapy to each individual's genetic and molecular blueprint is turning into standard practice. The integration of pharmacogenomics into everyday medicine doesn't just represent scientific progress—it symbolizes a philosophical shift toward a more humane, precise, and proactive approach to healthcare. In the coming decade, personalized cardiovascular therapy will no longer be an experimental concept but the new frontier of modern medicine.

Figure 1: Schematic diagram showing how pharmacogenomic testing guides antihypertensive and heart failure therapy toward precision medicine.

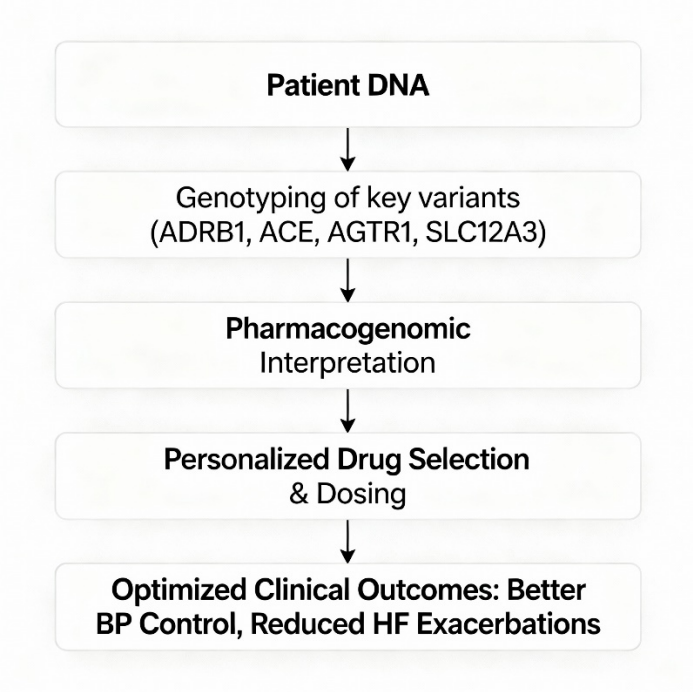

Table 1. Gene–Drug Associations in Hypertension and Heart Failure

Gene	Polymorphism	Associated Drug/Class	Clinical Effect	Outcome	Reference
ADRB1	Arg389Gly	β-Blockers (Metoprolol, Bisoprolol)	Alters receptor activity	Arg389 → better response	41
ADRB2	Gly16Arg, Gln27Glu	β-Blockers	Modulates vasodilatory response	Glu27 → improved HF outcomes	42
ACE	I/D	ACE inhibitors (Enalapril, Ramipril)	Affects ACE plasma levels	D allele → enhanced efficacy	43
AGTR1	A1166C	ARBs (Losartan, Valsartan)	Influences receptor binding	C allele → reduced response	44

SLC12A3	rs13306673	Thiazide diuretics	Alters NCC activity	Variant → altered natriuresis	45
NPR3/MME	Various SNPs	Sacubitril/Valsartan	Regulates natriuretic peptides	Affects response & BNP levels	46

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