Review Article

Personalised Medicine in Cardiovascular Pharmacology: A Review of advances in Pharmacogenomics and Drug Development

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ABSTRACT

With an estimated 20.5 million deaths from cardiovascular diseases (CVDs) in 2021, around 80% of these deaths will occur in low- and middle-income countries, making CVDs the leading cause of mortality worldwide. Multiple risk factors, such as chronic inflammation, oxidative stress, hyperglycemia, and hyperlipidemia, are implicated in the etiology and pathogenesis of CVD. Mitochondria, the principal sites of reactive oxygen species (ROS) production and where ATP is synthesized, are pivotal for cardiovascular pathophysiology and are now leading targets of therapy. Lifestyle modifications and diet are first addressed in CVD, but drug therapy and surgery can significantly increase how long and how well patients with CVD live. Though orthodox pharmacotherapy has been used in medical settings for over 2,500 years, it does not offer a comprehensive integrative therapeutic method which is considered cost effective for the management of CVD and other chronic diseases. Thus, the need for more integrative methods such as pharmacogenomics. Pharmacogenomics, which explores how genetic diversity affects drug response, have strongly emerged in cardiovascular medicine. Genetic polymorphisms significantly affect the safety and efficacy of numerous drugs, such as antiplatelets, anticoagulants, statins, and antiarrhythmics. Critical genetic variants in the genes CYP2C9, CYP2C19, VKORC1, and SLCO1B1 govern the response to warfarin, clopidogrel, simvastatin, and other medicines. Notably, the CYP2C19 genotype influences the pharmacokinetics and safety of mavacamatem, an emerging treatment for hypertrophic cardiomyopathy. In low-resource settings, the application of pharmacogenomic testing is limited by many barriers such as cost, unavailability of trained scientists, limited laboratory infrastructure, and the absence of population-based genomic data. Ethical and regulatory issues—such as unclear clinical guidelines and data privacy concerns—further hinder adoption. To unlock the global potential of personalized cardiovascular therapy, strategic investment in infrastructure, inclusive genomic research, and supportive health policies are essential. With coordinated efforts, pharmacogenomics can enhance therapeutic precision and advance global health equity.

Keywords: Diabetes; Precision medicine; Cardiovascular therapy; inflammation; Pharmacogenomics.

Introduction

Personalized medicine is a swiftly advancing area in healthcare, which relies on teams from various disciplines and on integrated technologies (such as clinical decision support) to apply molecular insights into diseases and improve preventive methods [1,2] The focus has shifted from reactive to preventative care as a result of advancements in human genome research, which now enable medical practitioners to develop optimal care regimens at every stage of a disease [3]. Words such as stratified medicine, customized medicine, personalized medicine, and individualized medicine are frequently used interchangeably, implying highly personalized pharmacotherapy (that is, targeted drugs on the basis of distinct genetic profiles). Furthermore, personalised medicine is frequently associated with ideas like predictive, preventative, and protective medicine.

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Pharmacogenomics examines how a person's genetic composition influences his or her reaction to medications. The term merges "pharmacology" and "genomics," indicating the convergence of drug science and genetics [4-6]. There is potential in this field for creating customised drugs that take into account an individual's genetic makeup. Although environmental factors, diet, age, lifestyle, and overall health also impact drug responses, genetic variations are critical for enhancing drug effectiveness and safety [4]. An individual's response to a medication, whether positive or negative, is a complex characteristic shaped by multiple genes. In the past, predicting drug responses was difficult because of the unidentified genetic factors involved. Nonetheless, the identification of minor genetic variations—especially single nucleotide polymorphisms (SNPs)—has made it feasible to conduct genetic testing for predicting drug responses [5].

Conventional pharmaceutical sciences, such as pharmacogenomics, are combined with biochemistry, with understanding of proteins and genes, and SNPs. The human genome is believed to contain approximately 11 million SNPs, which occur approximately once every 1,300 base pairs, making them the most frequently examined genetic variations in pharmacogenomics [4, 6]. Pharmacogenomics has the potential to reduce overall healthcare expenditures by decreasing unfavourable responses to medications; unsuccessful drug trials; the duration needed for a medicine to be approved; the duration of medication use; the number of medications needed to identify an effective treatment; and the impact of diseases on the body through early diagnosis [7].

This review intends to investigate recent advancements in pharmacogenomics and drug development within cardiovascular pharmacology, emphasizing their ability to improve treatment results, reduce adverse effects, and enhance overall healthcare efficiency. The purpose of this review is to underscore the transformative influence of personalized medicine in cardiovascular care by examining current research and clinical applications. The rationale for this review is to add to the pool of knowledge on how individual variability in drug responses greatly influences the efficacy and safety of cardiovascular therapies.

The Role of Pharmacogenomics in Cardiovascular Pharmacology

Personalized medicine objectives for optimization. Disease classification, amplification of diagnostic accuracy, and personalized treatment aimed at precise disease subtypes and human-specific health conditions. Optimising drug selection and dose is a key element of cosmopolitan treatment methods. Pharmacokinetics and pharmacodynamics have significant effects on the way an organism reacts to medicines. Pharmacokinetics is the study of time-varying changes in drug concentrations during absorption, distribution, metabolism, and elimination. Pharmacodynamics the biochemical and physiological effects of drugs as well as their mechanism of action in body. Example are drug interactions on the receptor binding, effects on target cells, and subsequent therapeutic effects [8]. Pharmacogenomics involves the study of genes and how an individual response is affected due to drugs Due to variability existence among individuals against drug therapy response, itis a challenging task to predict the degree of effectiveness of a medication to a particular patient. Although the most recent pharmacogenomic trial used in the clinical context has focused on drug metabolism. Pharmacogenomic trials have focused on warfarin in relation to the CYP2C9 and VKORC1 genotypes, clopidogrel in relation to the CYP2C19 genotype, and simvastatin in relation to the SLCO1B1 genotype [9].

Key Pharmacogenomic Markers in Cardiovascular Medicine

Cytochrome P450 enzymes (CYPs)

Cytochrome P450 (CYP) enzymes are a superfamily of enzymes that play a crucial role in metabolizing drugs, toxins, and endogenous compounds. They are primarily found in the liver, but also in other tissues like the gut, kidneys, and lungs. [10]

CYPs are the major enzymes involved in human drug metabolism, accounting for up to 75% of drugs processed by enzymes. At least 57 CYPs, are encoded for by the human genome and these genes are organized into 18 families and 43 subfamilies. CYPs play important roles in the maintenance of general human health, particularly as they relate to the metabolism of pharmaceuticals. Of salient interest for CYPs in drug metabolism is the varying response of individual patients to administered pharmaceuticals. It is known that some individuals metabolize drugs relatively rapidly, while other individuals metabolize the same drugs relatively slowly. The differences of metabolism may be associated with the expression of CYPs, particularly in the liver and intestines. Some external factors, such as diet, prior exposure to other drugs, and tobacco and alcohol consumption have been suggested as influencing the expression and functional activity of CYPs that are closely related to endogenous substrates.

Among the 57 functional CYPs, the isoforms belonging to the CYP1, CYP2,

andCYP3 families are responsible for the metabolism of around 80% of clinical drugs [11]. These include CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5; with CYP3A4 and CYP2D6 contributing to over 50% of CYP-related drug metabolism [11]

Function of CYPs in Drug Metabolism

1. Phase I metabolism: introducing functional groups (-OH, -NH2, -SH) into lipophilic compounds, making them more water-soluble and easier to eliminate.
2. Drug inactivation: converting active drugs into inactive metabolites, reducing their therapeutic effects.
3. Toxin elimination: eliminating toxic substances, including environmental pollutants and carcinogens.

Genetic Variation and Influence on Drug Metabolism

The expression and activity of CYPs varies considerably among individuals and different populations. These Genetic variability in CYP genes has received great scientific attention as a basis for rationalizing individual differences over the last two decades. The polymorphisms of CYP genes are involved in multiple allelic variants, the frequencies of which vary among different populations. More than 350 functionally polymorphic CYPs have been collected. [12]. The greatest number of allelic variants are described for CYP2D6 (63alleles), CYP2B6 (28alleles), and CYP2A6(22 alleles). CYP2D6, as the most common mutant isoform, is involved in the metabolic process of nearly 25% of clinical drugs, and its polymorphisms can affect the metabolic process of about 50% of these. Accumulating evidence indicates that loss-of-function variants and gain-of-function variants are the two main types of genetic variation in CYP genes [13].

Loss-of-function variants, which frequently affect splicing and expression of CYP genes, may reduce elimination and enhance drug plasma concentrations, whilst gain-of-function variants, resulting from copy number variants with an increased number of functional gene copies, or promoter variants and amino acid variants with an increased substrate turnover of CYP genes, may enhance elimination and reduce drug concentrations [14].

There now are four types of phenotypical changes in CYPs that have been identified, including poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM), and ultra-rapid metabolizers (UM), which are attributed to drug response based on genetic variations in CYP genes. PM usually suffer more adverse reactions at a normal dose of drug, due to being homozygous for either functionally variant alleles or due to a complete deletion of the gene causing reduced enzyme activity [16]. IM is heterozygous for specific variant alleles. EM have two functionally competent alleles. UM with two or more active genes on the same allele often fail to respond to drugs at a normal dose. Therefore, genetic polymorphisms in CYP genes may play important roles in the optimization of drug treatments with respect to efficacy and prediction of adverse reactions [17].

Role of Gene and Single-Nucleotide Polymorphism (SNPs) Variation and The Individual Variability in Drug Metabolism

SNPs affects CYP450 enzyme activity in several ways including increased activity, leading to faster metabolism of certain drugs, decreased activity leading to slower metabolism and potential toxicity and altered substrate specificity of specific CYP450 enzymes, affecting the metabolism of certain drugs.[18]

The above phenomenon is exemplified in the role of CYP2D6 involved in metabolizing antidepressants (e.g., fluoxetine), antipsychotics (e.g., risperidone), and beta blockers (e.g., metoprolol) leads to increased activity. Whereas SNPs associated CYP2D6, CYP2D6, CYP2C9: involved in metabolizing warfarin, phenytoin, and tolbutamide and SNPs associated with CYP2C6, CYP2C9 CYP3A4: involved in metabolizing statins (e.g., atorvastatin benzodiazepines (e.g., alprazolam), and HIV protease inhibitors leads to poor metabolism and reduced metabolism respectively [19]

The clinical Implications of these includes enhanced possibilities of personalized treatment when genetic testing can inform treatment decisions and optimize drug therapy, minimizing adverse reactions when identifying genetic variants can help predict potential adverse reactions and guide dose adjustments and improving drug through application of Pharmacogenomics. [20]

Influence of Metabolism of Specific Drugs on Drug Response in Clinical Practice

Clopidogrel—CYP2C19 genotype

Clopidogrel acts as a prodrug, and its curative efficiency depends on its enzymatic conversion to the active thiol metabolite H4 [22]. While most of the prodrug is hydrolyzed to an inactive byproduct, its own bioactivation takes place in a two-step process involving several CYP isozymes [23]. CYP2C19 primarily interferes with these two

metabolic processes, leading to the formation of H4, whereas CYP3A4 contributes to the formation of H4 to a lesser extent.

Several studies have examined the biological variation in the CYP enzyme that affects the ability of clopidogrel to suppress platelets. The most stable result is that loss-of-function individual nucleotide polymorphisms (SNPs) in CYP2C192 (rs4244285) and CYP2C193 (rs4986893) result in decreased platelet restraint, increased platelet responsiveness, and an increased risk of significant cardiovascular complications, including stent thrombosis, in individuals undergoing PCI [24]. A meta-analysis of nine studies suggested a gene-dose result surrounded by a discrepancy for the fusion of cardiovascular events: a cy carrier has a hazard ratio of 1.57 (95% confidence range 1.13–2.16), whereas a person with a pair of reduced-function alleles has a much greater liability (hazard ratio 1.76, 1.24–2.5) [25]. The CYP2C19 17 (rs3758581) polymorphism adds to the enzyme task, which increases the risk of bleeding while also improving efficacy and CV outcomes [25]. The above findings prompted the FDA to revise the clopidogrel labeling together with a box warning stating that caution should be exercised with the reduced function of the CYP2C19 allele.

Table1.Human CYPs diversity and functions.

CYP Family	Primary Functions	Subfamilies	Genes
1	Drug metabolism	3	3
2	Drug/steroid metabolism	13	16
3	Drug metabolism	1	4
4	Arachidonic acid/fat metabolism	5	12
5	Thromboxane synthase	1	1
7	Steroid 7α-hydroxylase	2	2
8	Bile acid biosynthesis	2	2
11	Steroid biosynthesis	2	3
17	Steroid 7α-hydoxylase	1	1
19	Aromatase	1	1
20	Undetermined function	1	1
21	Steroid biosynthesis	1	1
24	Vitamin D deactivation	1	1
26	Retinoic acid hydroxylase	3	3
27	Bile acid biosynthesis	3	3
39	Undetermined function	1	1
46	Cholesterol 24-hydroxylase	1	1
51	Lanosterol 14α-demethylase	1	1

Angiotensin-Converting Enzyme (ACE)

One of the most popular drugs for treating cardiovascular and renal diseases, such as hypertension, diabetes, nephrotic syndrome, heart failure, and acute coronary syndrome, are angiotensin-converting enzyme inhibitors (ACEIs) [26]. In those with hypertension and normotension, ACE inhibitors successfully lower mean arterial pressure in addition to systolic and diastolic blood pressure [27, 28]. Numerous randomized controlled trials have evaluated their effectiveness as antihypertensive agents. One of the four first-line medication classes for people with high blood pressure is ACE inhibitors, according to evidence-based guidelines for managing hypertension published by the Eighth Joint National Commission (JNC8) in 2014 [29]. Only thiazide diuretics and calcium channel blockers are advised for the Black population, although the other three classes—calcium channel blockers, thiazide diuretics, and angiotensin receptor blockers—are appropriate for the general non-Black population [30].

Guidelines from the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC) also recommend ACE inhibitors as first-line antihypertensive treatments, particularly for patients with cardiovascular disease and diabetes mellitus Although ACE inhibitors are helpful, Black hypertension patients have not responded as well to them in clinical settings as white patients [31].ACE inhibitor medication has been demonstrated to considerably lower overall mortality since the 1980s in a number of large, prospective, randomised, placebo-controlled trials, particularly in patients with heart failure with a reduced ejection fraction (HFrEF) . Additionally, these trials showed that even in patients with left ventricular failure who do not exhibit any symptoms, ACE medications reduce mortality rates. ACE inhibitors remain the preferred initial treatment for patients with heart failure in view of these strong findings [32]. By decreasing systolic wall stress, preload, and afterload, ACE inhibitors increase cardiac output without raising heart rate, improving the outcomes of heart failure. Additionally, they enhance the hypertrophy of cardiac myocytes [34].

Angiotensin II is essential for cardiovascular regulation because it causes precapillary arteriole

and postcapillary venule vasoconstriction, inhibits norepinephrine reuptake, promotes catecholamine release from the adrenal medulla, reduces sodium and water excretion, promotes aldosterone synthesis and release, and promotes the hypertrophy of cardiac myocytes and vascular smooth muscle cells [35].

In addition to effectively reducing preload and afterload by lowering arterial and venous pressure, ACE inhibitors also work by blocking the angiotensin-converting enzyme, which is responsible for converting angiotensin I into angiotensin II. Another mechanism that has been proposed is that ACE inhibitors interfere with the breakdown of bradykinin, a peptide that induces vasodilation, which results in reduced production of angiotensin II, promotes natriuresis, lowers blood pressure, and prevents remodeling of cardiac myocytes and vascular smooth muscle [36].

Warfarin-Sensitivity Genes (VKORC1 & CYP2C9)

A significant period of time must transpire before perfect anticoagulation with warfarin medication may be obtained, both among different individuals and within the same species, as well as when the drug is replaced with other medicines. Pharmacogenetic modeling of the variability observed in warfarin treatment is based on the interaction between CYP2C9 and VKORC1. The second reaction of humans to warfarin is determined by a heritable mutation in the VKORC1 gene, which controls the oxidation status of vitamin K, whereas the CYP2C9 gene contributes to the transformation of S-warfarin. Pharmacists with experience in cardiology medicine control have been assigned by a number of organizations, including our group, to recommend starting dosages of warfarin that ensure both safety and effectiveness [37].

The warfarin label is approved by the U.S. According to the Food and Drug Administration (FDA), individuals with the VKORC1 genotype, which is linked to enhanced drug sensitivity, and the CYP2C9 genotype, which is linked to slower drug clearance, should be given lower-than-normal dosages of warfarin. The Pharmacogenetics Applications Consortium (CPIC) has created a pharmacogenomic algorithm that integrates CYP2C9/VKORC1 genotyping consequences with clinical factors equivalent to age and pressure, for the purpose of advising on the choice of medicines. Consequently, several establishments, including ours, have approved a genotype-based warfarin dosage as standard practice [37].

Beta-Adrenergic Receptors (ADRBs)

Beta-blockers compete with catecholamines for binding to the β1-adrenergic receptor, acting as emies. Angina, myocardial infarction, cardiac arrhythmia, and excessive blood pressure are among the conditions for which they are typically prescribed. Several genes, including CYP2D6, ADRB1, and ADRB2, have been linked to variations in human β-blocker responses. The unfavorable metabolite profile of blockers such as propranolol, timolol, and metoprolol is correlated with differences in CYP2D6 function. Increased drug levels in the circulation occur in 5–10% of the societal transport pair, who also possess a greater loss-of-function CYP2D6 allele 39]. However, CYP2D6 polymorphism does not always result in noteworthy clinical outcomes. For example, carvedilol has no effect on CYP2D6 metabolism, whereas several blockers favor atenolol and nadolol. Various conclusions have been drawn from investigations into how common ADRB1 differences affect the blocker response [40]. While some studies have found no significant correlation, others have demonstrated that individuals homozygous for the Arg389 allele have a higher left ventricular ejection fraction than those homozygous for the Gly389 allele do [41]. Neither evidence from cellular probes nor changes in clinical outcomes [42] have been linked to common biological variations in ADRB2.[43]

The FDA's warning about the ambiguous relationship between CYP2D6 hereditary variation and blocker success is reflected in the label for Lopressor (metoprolol tartrate), which states that CYP2D6-dependent metabolism has no significant effect on the product's secondary safety or tolerability. However, patients with heart failure who retain the loss-of-function CYP2D6 allele may be at increased risk of excessive drug accumulation and may need to avoid blockers; for a more focused approach to monitoring blocker therapy, pharmacogenomic interactions between blockers and heritable ADBR1 discrepancies may be observed [44].

Statins

3-Hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) is the enzyme that limits the rate at which cholesterol is synthesized in the liver. By blocking HMGCR, statins, a commonly prescribed type of cholesterol-lowering medication, lower the levels of low-density lipoprotein (LDL) and circulating cholesterol. Many people use statins to avoid CVD, both directly and indirectly because of this mechanism. Significant interindividual diversity in response has been noted, although massive randomized controlled trials (RCTs) have continuously demonstrated their effectiveness. In certain people, this variability may result in inadequate cholesterol reduction and an inability to

avoid cardiovascular events [45]. To further understand the genetic basis of this variance in statin efficacy and tolerance, pharmacogenomic studies have been conducted [45].

Role of Transporters and Regulatory Guidance

Strong evidence supports the role of pharmacogenetic variation in drug transporters in influencing the statin response [46]. However, evidence for ancestry-specific genetic markers that predict both lipid-lowering efficacy and cardiovascular risk reduction remains limited and inconclusive. Some research groups have proposed the use of transporter gene polymorphisms to guide individualized statin dosing [46].

The SLCO1B1 gene, in particular, has been well studied. Its SLCO1B15 allele is closely linked to a higher incidence of myopathy brought on by simvastatin, and this association has been replicated across multiple clinical trials. While similar associations have not yet been established for other statins, the U.S. Food and Drug Administration (FDA) has responded by revising the simvastatin prescribing label, recommending alternative therapies for patients homozygous for SLCO1B15, and advising against prescribing 80-mg doses of simvastatin in this group.

Global Regulatory Support for Pharmacogenomics

Since 2013, the FDA has encouraged the integration of pharmacogenomics (PGx) into early clinical drug development. In parallel, the European Medicines Agency (EMA) has revised its guidelines to incorporate DNA sample collection and genomic data throughout all phases of clinical development [47]. According to research, drugs with supporting genetic evidence have a clinical success rate that is more than double that of those without such evidence [48].

Rosuvastatin

Rosuvastatin has been identified as a substrate for the efflux transporter BCRP, which is encoded by the ABCG2 gene and expressed on the apical membrane of hepatocytes. The ABCG2 421C > A polymorphism has been linked to rosuvastatin pharmacokinetics and an enhanced LDL-lowering response [68]. Notably, the observed LDL reduction in carriers of this variation was comparable to that achieved with double the usual rosuvastatin dose. Atorvastatin and simvastatin are largely metabolized by CYP3A4, and frequent polymorphisms in CYP3A4 may alter their pharmacokinetics and therapeutic response. Statin medication also leads to the overexpression of the LDL receptor (LDLR) [49] LDLR haplotypes have been linked to decreased statin efficacy in populations with African heritage. Additionally, in a combined GWAS of three trials, carriers of the rs8014194 polymorphism in the CLMN gene, which encodes the calmin protein of uncertain function, presented a 3% greater reduction in total cholesterol than noncarriers did [50].

Clinical Implementation

The most robust evidence supporting the clinical relevance of statin pharmacogenetics pertains to genetic variations in drug transporters. However, strong evidence for other genetic markers associated with statin response and myopathy risk remains limited and requires further validation. As a result, several research groups have advocated the use of transporter polymorphisms to guide statin dosing [51]. The U.S. Food and Drug Administration (FDA) has updated the label for simvastatin to incorporate SLCO1B1-defined guidelines, advising prescribers to avoid prescribing 80 mg of simvastatin to homozygous SLCO1B15 carriers and to consider alternative statin options, although the association between the SLCO1B15 genotype and simvastatin-induced myopathy has been confirmed in multiple clinical studies (although similar associations with other statins are less well established). Summary of key pharmacological markers in cardiovascular medicine are provided in Table 1.

Table 2: Key Pharmacogenomic Markers in Cardiovascular Medicine

Pharmacogenom Marker	Drug(s) Affecte	Clinical Significance
CYP2C19	Clopidogrel (antiplatelet)	Variants influence activation of clopidogrel → affects platele inhibition and risk of thrombosis.
SLCO1B1	Statins (e.g., Simvastatin)	Variants associated wit statin-induced myopathy and altered drug transport.
VKORC1	Warfarin	Affects sensitivity to warfarin → dosing adjustments needed to reduce bleedir risk.

Pharmacogenom Marker	Drug(s) Affecte	Clinical Significance
CYP2C9	Warfarin	Variants reduc drug metabolism → higher bleedin risk at standar doses.
ADRB1 & ADRB2	Beta-blockers (e.g., Metoprolc	Influence efficacy and side-effect profiles of bet blocker therap
ACE (Angiotensin-Converting Enzyme)	ACE inhibitors, antihypertensiv	Polymorphism affect blood pressure contr and response t ACE inhibitor
AGT (Angiotensinoge	Antihypertensiv therapies	Genetic variation linke to hypertensio risk and therap response.

Advances in Pharmacogenomic-Guided Drug Development

Targeted Drug Therapy

With a high attrition rate in drug development, in which more than 90% of drugs fail during the process [52], effective methods are needed to increase success rates. Studies have shown that drugs supported by genetic evidence have more than twice the likelihood of clinical success. In 2013, the FDA issued industry guidance on clinical pharmacogenomics (PGx) and early-phase clinical studies [53]. Both the European Medicines Agency (2018) and the FDA (2013) have recommended the collection of DNA samples throughout all phases of clinical development. The genomic characterization of clinical trial participants has become standard practice, with approximately 80% of Industry Pharmacogenomics Working Group (I-PWG) members reporting the use of next-generation sequencing [54]. While relatively few studies have focused on traditional PGx markers related to drug metabolism, there is a growing emphasis on biomarkers for targeted therapy, a key aspect of precision medicine.

Most genetic characterization of trial participants occurs in oncology studies, although other therapeutic areas—including cardiovascular diseases, neuroscience, immunology, and rare diseases—are also increasingly incorporating genomic insights.

Integrating pharmacogenomic data into a clinical trial design allows for a more personalized approach to drug evaluation. By identifying genetic subgroups with a greater likelihood of responding to a specific treatment, researchers can develop more efficient and targeted trials, ultimately reducing both the time and cost associated with drug development [55].

Biomarker-Driven Clinical Trials

The mapping of the human genome and developments in next-generation sequencing (NGS) have been major factors in the development of precision medicine. The capacity to swiftly and thoroughly identify genetic traits, including mutations, rearrangements, and copy number changes, has significantly improved due to advancements in sequencing technologies [56]. Understanding possible biological phenotypes in diseases and working to target these phenotypes specifically served as the foundation for precision medicine.

Precision medicine, in which treatments are customized according to genetic changes, has advanced as a result of these developments. For instance, almost 36% of patients with advanced malignancies had treatable genetic alterations, according to a prospective clinical sequencing study of 10,000 patients at the Memorial Sloan Kettering Cancer Centre (MSKCC) [57]. Additionally, advances in drug development that target genetic changes specific to a disease have aided in the expansion of biomarker-guided therapies, which began in oncology but have since spread to other clinical areas, such as diabetes, CVD, kidney disorders, and neurological conditions [58].

Gene editing technologies: The roles of CRISPR-Cas9

CRISPR-Cas9 has transformed translational medicine by bridging the gap between basic research discoveries and therapeutic applications. Although new insights into how genes work have changed treatment approaches, problems such as off-target effects and limitations in altering particular genomic regions still plague gene editing technology. However, the development of CRISPR-Cas9 offers a potential remedy. Because it allows for precise gene editing, this extremely adaptable technology is especially useful for the genomic alterations needed for clinical interventions [59].

Important risk variables like inflammation, arterial calcification, and plasma lipoprotein levels are influenced by genetic differences, including mutations and frequent polymorphisms. Heritability estimates for coronary atherosclerosis, which are based on fatal cardiac events, range from 38% to

57%, which is further supported by twin studies [60]. Genetic factors play crucial roles in many cardiovascular diseases, making them strong candidates for CRISPR-Cas9-based therapies. The heritability estimates for advanced atherosclerosis, the primary cause of coronary artery disease (CAD), ranges from 40% to 70%, indicating a significant genetic contribution to disease pathology [61].

Genomic editing has considerable potential for directly correcting single-gene abnormalities that contribute to certain CVDs, presenting a promising approach for therapy and even the potential eradication of specific disease forms [62]. Furthermore, the development of CRISPR-Cas9 systems that rely on transitory protein regulation rather than permanent genetic modifications has increased the therapeutic value of these methods. The successful insertion of advantageous genes into early human embryos at the zygote stage [63] indicates that the use of CRISPR-Cas9 in human systems is feasible. The main uses of CRISPR-Cas9 are examined in this section, with an emphasis on mitigating mitochondrial dysfunction, controlling protein expression, and fixing genetic abnormalities.

Use of CRISPR-Cas9 in CVD

Therapeutic use of CRISPR-Cas9 in CVD represents an evolutionary advance in precision medicine, as it allows direct editing of disease-causing pathogenic genetic variants [64]. Multiple cardiovascular diseases have distinct inheritance, with certain genes playing key roles in their etiology and progression. Familial hypercholesterolemia (FH), for instance, is strongly linked with mutation in the lipoprotein receptor gene LDLR and is one of the most important targets for heritable genome editing [65]. Since low-density lipoprotein (LDL) is directly implicated in the development of

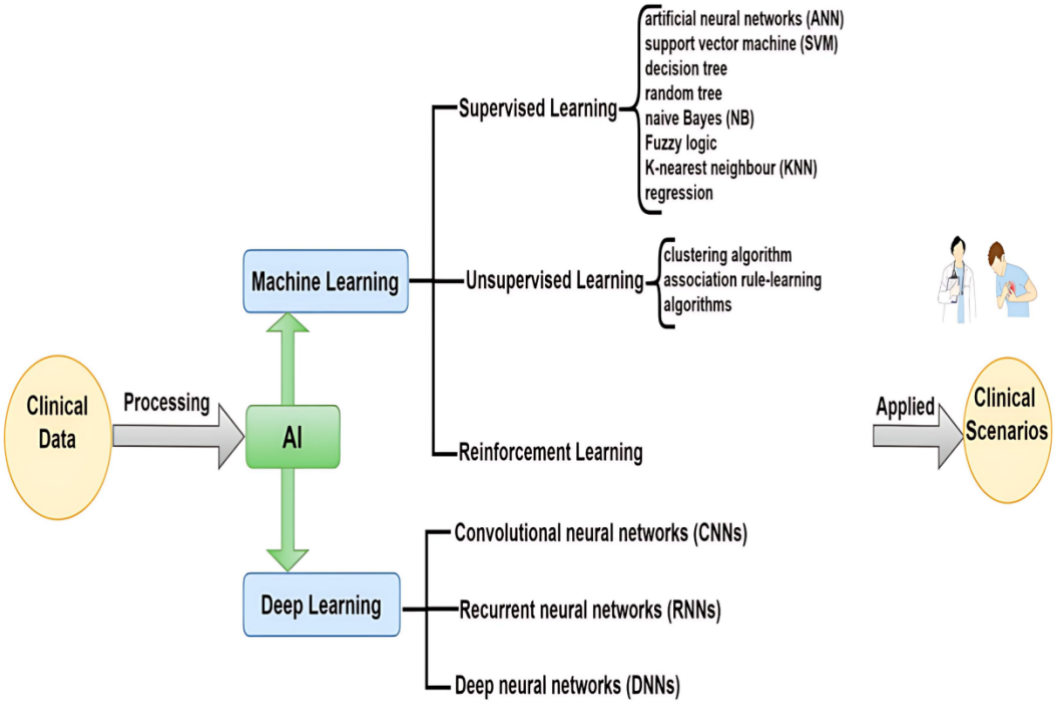
therapies lowering LDL have immense therapeutic power in lowering overall cardiovascular risk. Management of atherosclerosis—a systemic inflammatory vascular condition that accounts for more than one-quarter of global mortality—requires drugs that, concurrently, reduce LDL and triglycerides and elevate protective high-density lipoproteins (HDL) [66,67]. Atherosclerosis is characterized by the accumulation of fibrofatty plaques in vessel walls, and left untreated, can progress to fatal states such as ischemic stroke, myocardial infarction, peripheral artery disease, and even psychological distress related to chronic illness [68].

One of the more well-characterized FH-associated mutations is LdlrE208X, the murine homologue of the human E207X mutation. This nonsense mutation creates an early stop codon, interfering with LDL receptor function, lowering LDL clearance, and enhancing atherosclerosis. In a model study, Zhao et al. used adeno-associated virus serotype 8 (AAV8) to deliver CRISPR-Cas9 to a mouse model carrying this mutation. The therapy partially restored LDL receptor function, reduced macrophage infiltration, lessened plaque area, and exhibited a dramatic reduction in total cholesterol, LDL, and triglycerides, all without major off-target effects, thereby establishing efficacy and safety [69].

Outside of FH, CRISPR-Cas9 has been successfully used in genetic cardiomyopathies.

Dilated cardiomyopathy (DCM), found in

Figure 1: Application of AI in Clinical Practice [86].



contractility, and high mortality [70]. One of the largest advances was the creation of the ABEmax-VRQR-SpCas9 base-editing platform, which was used to edit disease-inducing mutations within the RBM20 gene (particularly RBM20R634Q and RBM20636). Editing iPSCs and grafting them into mouse heart tissue corrected pathologic dilation, restored contractile function, and prolonged survival, while untreated models experienced progressive ventricular enlargement [71]. Editing the TTN gene encoding titin also corrected function of sarcomeres in human iPSC-derived cardiomyocytes, further illustrating the potential of CRISPR to correct structure and function deficits [72].

CRISPR has also revealed viral cardiomyopathy mechanisms. Genome-wide screens identified ADAM9, a metalloproteinase necessary for EMCV infection, as a therapeutic target [73]. In hypertrophic cardiomyopathy (HCM), CRISPR-Cas9 was employed to knock out the MYH6 R403Q mutation using AAV9 vectors, deleting the defective allele in over 70% of cardiomyocytes and halting disease progression [73,74]. Some of the other examples include the correction of LZTR1 Noonan syndrome mutations, MYBPC3 embryonic mutation correction that is linked with HCM [75], and therapeutic PRKAG2 allele knockout in cardiac syndromes [76]. In addition, AAV9-delivered CRISPR elimination of the RYR2 R176Q allele suppressed catecholaminergic polymorphic ventricular tachycardia (CPVT), and PLN R14del mutation correction normalized calcium control and reduced arrhythmogenic risk [77].

Finally, CRISPR has been directed against Duchenne muscular dystrophy (DMD), a fatal X-linked illness defined by dystrophin deficiency [78]. Using AAV9 vectors and an engineered CRISPR system to induce exon skipping, researchers corrected as much as 90% of dystrophin expression in cardiac muscle, improving cardiac and skeletal muscle function. Significantly, gene correction was observed following four weeks, emphasizing the rapid therapeutic response of CRISPR-Cas9 against deforming inherited disorders.

Learning and Artificial Intelligence (AI)

Pharmacogenomics, the study of how a human's inherent makeup affects his or her response to a medicinal product, is a key avenue for advanced personalized medicine. However, the integration of pharmacogenomic knowledge into the clinical workflow is hindered by significant impediments, including difficulties in data collection, decision-making, and execution [79]. The related interactions among genes and drugs highlight the need for sophisticated instruments to predict and determine the manner in which individuals respond to multiple medicines [80]. In light of the above, intelligent automation (automated reasoning) and machine learning are essential opportunities to overcome the obstacles mentioned above and accelerate the development of personalized healthcare services [80].

Role of Artificial Intelligence (AI) in Enhancing Cardiovascular Pharmacotherapeutics

AI methods are rapidly transforming cardiovascular pharmacotherapeutics by enhancing diagnostic accuracy, predicting patient outcomes, and personalizing treatment strategies. By analysing medical history, biomarkers and genetic information found in huge patients' database, response to certain treatments can be effectively predicted. In addition, machine learning algorithms can identify key predictors of treatment response, such as SOX5, dP/dtmax, and cTnT, allowing for more targeted therapies [81]

Furthermore, AI can help personalize treatment plans by analyzing individual patient characteristics, such as genetic profiles and medical histories through identifying specific biomarkers and genetic variants associated with cardiovascular disease, thereby aiding in developing tailored treatment strategies.[82]

Finally, AI improves diagnostic accuracy and enhances patient outcomes. A very illustrative example is in its application to predict optimal therapeutic doses of a number of CV medicines, including clopidogrel, warfarin, and lipid-lowering medicines, notably simvastatin, are currently being studied as curative targets [83].

AI application have shown a significant discrepancy between the dose of warfarin currently given and the various biovalable concentration in different cohorts , as demonstrated by the randomized clinical trials performed by Pirmohamed et al. and Syn et al. Pirmohamed et al. have revealed that patients who have received a warfarin dose established on a pharmacogenetic basis remain within a curative transnational normalization ratio (INR) variety longer than those receiving standard doses [84].

AI has developed innovative systems for measuring cardiovascular risk and heart disease, managing hypertension, and improving pharmacologic

therapy. Shah et al. implemented corrective medicine approaches to clarify the mechanism underlying cardiac catastrophe and revealed a recent classification of emotion failure together with preserved expulsion fraction (HFpEF) [85]. This classification was improved by the use of "phenomapping"', an AI-based unsupervised deep learning technique that combines extensive tolerant facts, including clinical evaluation, laboratory consequences, echocardiogram, and image analysis.

There are still new opportunities for drug research and optimization thanks to machine intelligence. See Figure 1 and Table 2. By combining various patient, pharmacogenomic, and population-level data into meaningful insights for healthcare delivery, AI is transforming clinical practice. Precision diagnosis, risk assessment, and therapy optimization is made possible in cardiovascular medicine by AI-driven algorithms that evaluate complicated datasets like imaging, genetic profiles, laboratory results, and electronic health records.

Challenges and Future Directions

The future of customized medicine for cardiovascular pharmacology is being shaped quickly by advancements in pharmacogenomics to provide more individualized and effective treatments on the basis of specific genetic backgrounds. As the disease burden of cardiovascular diseases (CVDs) continues to increase globally, particularly in aged and high-risk populations, there is an urgent need to shift from a "one-size-fits-all" treatment strategy to more personalized strategies. Pharmacogenomics will significantly contribute to this revolution through the discovery of genetic variations that influence drug metabolism, drug response, and the risk of adverse effects. For example, polymorphisms in CYP2C19, SLCO1B1, and VKORC1 have been shown to significantly influence how patients respond to frequently prescribed cardiovascular drugs such as clopidogrel, statins, and warfarin, respectively. The integration of genetic testing into clinical practice has the potential for tailoring drug selection and dosing, improving treatment responses, and minimizing side effects.

Table 2: Artificial Intelligence's Use in Cardiovascular Research and Medicine

Category	Examples of Data Applications
Individual-Specific Data	Medical history, Laborato data, Family history
Pharmacogenomics Data	Drug–drug interactior Drug–gene interactior
Cohort & Populatio Data	Population /individual da stratification Medication da Environmental data, Adver effect profile, Populatic genetics
AI / Machine Learning Role	Integration and analysis heterogeneous data sources
Clinical Applicatior	Phenotyping (phenomapping), Pharmaceutical dr discovery, Cardiovascul imaging, Clinical practice

In addition to pharmacogenomics, ongoing innovations in drug development are also underpinning personalized medicine. New technologies such as next-generation sequencing (NGS), machine learning algorithms, and digital health platforms are enabling new genetic biomarkers and drug targets to be discovered. Moreover, expanding the use of adaptive clinical trials and biobank-related research studies is accelerating the identification of genotype-guided therapies. All these factors are set to enhance cardiovascular drug pipelines and enable more preventive, predictive, and precise models of care.

However, despite the clear benefit of pharmacogenomic-guided treatment, pharmacogenomic-based individualized medicine in low-resource environments faces several significant challenges, which undermine global health equity. There are no laboratory facilities or experts required to perform genomic tests and interpret them in such low-resource regions. Pharmacogenomic testing remains expensive and is reimbursed only infrequently by private and public health insurance, making it inaccessible to most patients. Additionally, population-level genomic information is limited, especially among African, Latin American, and indigenous populations, which reduces the validity and usability of genetic markers among these populations.

Policy and regulatory gaps also hinder implementation. Few or no national guidelines exist in most low-income countries for the incorporation of pharmacogenomics into care as routine, and ethical concerns, such as data protection and informed consent, are underemphasized. Pharmacogenomic education and knowledge among clinicians are lacking, further constricting clinical implementation. Practical concerns, such as time delays in reports, lack of point-of-care testing, and difficulty in sample transportation and storage, also affect the practical utility of pharmacogenomic tests.

To bridge this gap, future initiatives must focus on building infrastructure, reducing costs, doubling population-specific research, and developing clear policies and education systems. International collaborations, public–private partnerships, and investment in digital and handheld genomic technologies can make pharmacogenomic testing more sustainable and accessible in resource-limited settings. Facilitating equitable access to personalized cardiovascular medicine will be crucial in enhancing outcomes and reducing the global burden of CVDs.

Conclusion

Customized medicines in cardiovascular pharmacology may constitute a revolutionary strategy to increase tolerance on the basis of advances in drug discovery and pharmacogenomics. This area has the possibility of changing the method of care via hereditary realizations and AI-powered anticipatory models, improving the efficacy of medicinal products with reduced side effects. Data integration, moral concerns, and limitations on access to information continue to be studied, and technical progress is advancing toward closing these gaps in the face of challenges. Pharmacogenomics, as well as electronic health data and regulatory innovations, will further enhance the clinical use of precision medicine. As personalized medicine develops, it has the potential to innovate cardiovascular pharmacotherapy by providing patient-specific, safe, and more effective medicines that improve long-term health outcomes.

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Conflict of Interests

The authors declare that they have no conflicts of interest.

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