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# Personalized Medicine in Cardiovascular Pharmacology: 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. TCM, which has been used in medical settings for over 2,500 years, offers an integrative therapeutic method of treatment and has been found to be effective for the management of CVD and other chronic diseases. These integrative methods, along with pharmacogenomics, which explores how genetic diversity affects drug response, have emerged into 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 mavacamate, an emerging treatment for hypertrophic cardiomyopathy. In low-resource settings, the application of pharmacogenomic testing is limited by many barriers. These are cost, the 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

## 1. 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.

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 the increasing awareness that individual variability in drug responses greatly influences the efficacy and safety of cardiovascular therapies.

## 2. 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. Optimizing 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, circulation, metamorphosis, and elimination. Pharmacodynamics analyses drug interactions at a fixed concentration identical to that used for receptor binding, effects on target cells, and subsequent effects [8]. Pharmacogenomics involves ancestral variation affecting the abovementioned procedures, although the most recent pharmacogenomic trial used in the clinical context has focused primarily on drug metamorphosis. Pharmacogenomic trials have focused mainly 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].

### 2.1. Key Pharmacogenomic Markers in Cardiovascular Medicine

#### 2.1.1. Cytochrome P450 Enzymes (CYPs)

The liver enzymes' cytochrome P450 (CYP) group is essential for the metabolism of more than 30 individual drugs. Variability in the gene that codes for the enzyme may influence the productivity of the metamorphosis of the drug. Decreased or inactive CYP enzyme activity may result in reduced drug distribution and elimination, increasing the risk of drug accumulation and overdose. Soon after, scientists used inherited testing to identify the CYP gene variation for longitudinal monitoring and follow-up. Furthermore, pharmaceutical companies are looking into the manner in which their products are metabolized by various CYP enzyme differences [10].

Clopidogrel acts as a prodrug, and its curative efficiency depends on its enzymatic conversion to the active thiol metabolite H4 [11]. 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 [12]. 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 [13]. A meta-analysis of nine analyses (n = 9,685) 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) [14]. The CYP2C19 17 (rs3758581) polymorphism adds to the enzyme task, which increases the risk of bleeding while also improving efficacy and CV outcomes [14]. 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.

### 2.1.2. Clopidogrel—CYP2C19 Genotype

Clopidogrel is a medicinal product that requires metabolic activation to modify its thiol metabolite, which inhibits platelet activation and collection. The present metabolic method takes place several times, and the CYP2C19 enzyme facilitates this process simultaneously. The difference in CYP2C19 causing the enzyme shortage leads to decreased levels of the active thiol metabolite in circulation, which in turn diminishes platelet suppression. Additionally, they are more likely to experience severe adverse cardiovascular events, especially in those who have previously experienced percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS) [15]. Poor metabolizers, whose inherited dual nonfunctioning allele leads to an inactive enzyme, and intermediate metabolizers, whose individual nonfunctioning allele leads to a reduced enzyme product, are also included in the CYP2C19 polymorphism.

An expert panel study from the American College of Cardiology and American Heart Association in 2010 emphasised the impact of CYP2C19 transformation on the therapeutic effectiveness of clopidogrel. The present report played a role in the FDA's decision to add a warning label stating that persons who are needy metabolizers are likely to suffer subpar curative outcomes scheduled at low stages of the active metabolite. Pharmacogenomic testing is proposed as a way of analyzing persevering responses to the drug, and prasugrel and ticagrelor are recommended for underprivileged metabolizers, which do not depend on CYP2C19 metamorphosis [16]. Furthermore, the principles of the Clinical Pharmacogenetics Applications Consortium (CPIC) have amended the combination of underprivileged and intermediate metabolizers, together with the narrative of acute coronary syndrome (ACS) or transdermal coronary intervention (PCI) transition to other antiplatelet therapies. Although contemporary intelligence may be new, the FDA is not used

in academic writing, nor is it familiar with intellectual writing. Even though approximately 20% of patients who undergo PCI with stenting show a reduced response to clopidogrel, these patients are close to an increased risk of stent thrombosis, which can lead to serious fitness problems if not treated. Notably, several household protocols were familiarized within 2015 to screen patients undergoing cardiac catheterization via CYP2C19 pharmacogenomic testing. Similarly, companies such as the Florida Wellness Personalized Medicine Initiative have begun to introduce cosmopolitan CYP2C19 testing as standard practice for certain tolerant societies.

#### 2.1.3. 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) [17]. In those with hypertension and normotension, ACE inhibitors successfully lower mean arterial pressure in addition to systolic and diastolic blood pressure [18] [19]. Numerous randomized controlled trials have evaluated their effectiveness as antihypertensive agents [20]. 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 [21].

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 [22]. 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 [23] [24]. Although ACE inhibitors are helpful, Black hypertension patients have not responded as well to them in clinical settings as white patients [25].

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) [26] [27]. Additionally, these trials showed that even in patients with left ventricular failure who do not exhibit any symptoms, ACE medications reduce mortality rates [28]. ACE inhibitors remain the preferred initial treatment for patients with heart failure in view of these strong findings [29] [30]. By decreasing systolic wall stress, preload, and afterload, ACE inhibitors increase cardiac output without raising heart rate, improving the outcomes of heart failure [31]. Additionally, they enhance the hypertrophy of cardiac myocytes [32] [33].

**1) Mechanism of action**

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 [34] [35]. Uncertainty surrounds the precise mechanism of action of ACE inhibitors. The renin-angiotensin-aldosterone system is their primary target, however blood renin levels are not directly correlated with their actions.

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 remodelling of cardiac myocytes and vascular smooth muscle [36].

The ratio of angiotensin II's vasoconstrictive and salt-retentive effects to bradykinin's vasodilatory and natriuretic effects is regulated by the angiotensin-converting enzyme; ACE inhibitors change this ratio in favour of vasodilation and natriuresis by reducing angiotensin II production and postponing bradykinin breakdown. Although it is unknown how much substance P and other vasoactive chemicals contribute to the positive or negative effects of ACE inhibitors, they also have an impact on their metabolism [37].

#### 2.1.4. 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 [38].

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 [38].

#### 2.1.5. Beta-Adrenergic Receptors (ADRBs)

Beta-blockers compete with catecholamines for binding to the $\beta$1-adrenergic receptor, acting as enemies. 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 $\beta$-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] [40]. 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 [41] [42]. 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 [43] [44]. Neither evidence from cellular probes [45] [46] nor changes in clinical outcomes [47] [48] have been linked to common biological variations in ADRB2.

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 [49] [50]. 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 [51] [52].

#### 2.1.6. 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 [53]. To further understand the genetic basis of this variance in statin efficacy and tolerance, pharmacogenomic studies have been conducted [53].

**1) SLCO1B1**

The solute carrier organic anion transporting polypeptide 1B1 (OATP1B1), which is encoded by the SLCO1B1 gene and promotes the hepatic absorption of

statins from the portal circulation, is known to be a substrate of statins [54]. Previously known as OATP-C (also known as SLC21A6, OATP2, and LST1), our lab was the first to identify and introduce the nomenclature (range from 1a-14) for SLCO1B1 in 2001. We also determined the functional importance of this nomenclature [55]. Specifically, SLCO1B15 variation leads to decreased membrane localization of OATP1B1, and clinical studies have consistently associated this single-nucleotide polymorphism (SNP) with altered statin disposition. This leads to lower hepatocellular uptake and greater systemic drug exposure. In contrast, decreased plasma statin concentrations have been linked to the SLCO1B11b genotype.

Nonetheless, there is still debate on how well SLCO1B1 variations predict LDL-lowering effectiveness, which calls for more studies with bigger patient populations [56] [57]. Crucially, using statins can cause unanticipated muscle damage, which can range from minor myalgia to potentially fatal rhabdomyolysis. A recent genome-wide association study (GWAS) found that the SLCO1B15 allele is the most reliable predictor of simvastatin-induced myopathy, providing the strongest evidence to date [58]. According to this investigation, the odds ratio for the risk of myopathy caused by SLCO1B15 was 16.9 for homozygous carriers and 4.5 for heterozygous carriers [58].

Furthermore, in individuals on atorvastatin, simvastatin, or pravastatin, SLCO1B1 5 has been connected to statin-related adverse drug reactions (ADRs), including discontinuation, creatine kinase increase, and myalgia, as well as statin intolerance, which includes dose modifications and statin switching [59] [60]. All of these results show that SLCO1B1 SNPs affect the pharmacokinetics and pharmacodynamics of statins, which leads to statin-induced adverse drug reactions. Notably, different statins have different risks of myopathy; simvastatin has the highest risk, followed by atorvastatin, pravastatin, rosuvastatin, and fluvastatin [61]. In order to minimise the risk of statin-induced myopathy and optimise cholesterol-lowering medications, genotyping for SLCO1B1 SNPs may be helpful.

**2) HMGCR and APOE**

The pharmacodynamic response to statins, particularly the lowering of LDL, is influenced by genetic differences in HMGCR and APOE. According to LDL reduction, carriers of the HMGCR H7 haplotype, which is identified by three intronic SNPs (rs17244841, rs3826662, and rs17238540), demonstrated an 11% - 19% decreased sensitivity to statins [62]. These results, however, were not confirmed in a GWAS that looked into atorvastatin response [63]. It is currently unclear how the three main APOE haplotypes (rs429358 and rs7412) relate to the statin response. According to a preliminary GWAS on statin response, APOE polymorphisms affected the effectiveness of LDL-lowering medications, with the ε2 haplotype exhibiting the greatest response and variant carriers showing reduced efficacy [63], but a subsequent meta-analysis was unable to confirm these associations [64]. To fully understand how genetic differences in APOE and HMGCR affect the effectiveness of lipid-lowering medications, more re-

search is required.

**3) Kinesin-Like Family 6 (KIF6)**

A new mechanism affecting cardiovascular outcomes may be revealed by the KIF6 gene, a member of the kinesin-like family that has been connected to an elevated risk of coronary artery disease (CAD) [65]. Certain studies suggest that carriers of the rs20455 SNP in KIF6 may derive greater cardiovascular benefit from statin therapy than noncarriers do [66]. However, a meta-analysis involving major lipid-lowering trials revealed no substantial correlation between the risk of CVD and this SNP [67], nor did it reveal differences in statin efficacy between carriers and noncarriers. Thus, more investigation is required to clarify how KIF6 affects cardiovascular outcomes.

**a) Role of Transporters and Regulatory Guidance**

Strong evidence supports the role of pharmacogenetic variation in drug transporters in influencing the statin response [68]. 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 [68].

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.

**b) 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 [69]. According to research, drugs with supporting genetic evidence have a clinical success rate that is more than double that of those without such evidence [70].

Given the high attrition rate in drug development—where over 90% of investigational drugs fail to reach the market the adoption of genetically informed strategies is crucial to improving outcomes. In fact, approximately 80% of members of the Pharmacogenomics Working Group (I-PWG) report the use of next-generation sequencing (NGS) as part of standard practice in clinical trials.

**4) 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 ob-

served 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) [69] [70]. 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 non-carriers did [70] [71].

**5) 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 [58]. 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 1. Key pharmacogenomic markers in cardiovascular medicine.

| Pharmacogenomic marker | Drug(s) affected | Clinical significance |
|---|---|---|
| CYP2C19 | Clopidogrel (Antiplatelet) | Variants influence activation of clopidogrel—affects platelet inhibition and risk of thrombosis. |
| SLCO1B1 | Statins (e.g., Simvastatin) | Variants associated with statin-induced myopathy and altered drug transport. |
| VKORC1 | Warfarin | Affects sensitivity to warfarin—dose adjustments needed to reduce bleeding risk. |
| CYP2C9 | Warfarin | Variants reduce drug metabolism—higher bleeding risk at standard doses. |
| ADRB1 & ADRB2 | Beta-blockers (e.g., Metoprolol) | Influence efficacy and side-effect profiles of beta-blocker therapy. |
| ACE (Angiotensin-converting enzyme) | ACE inhibitors, antihypertensives | Polymorphisms affect blood pressure control and response to ACE inhibitors. |
| AGT (Angiotensinogen) | Antihypertensive therapies | Genetic variation linked to hypertension risk and therapy response. |

## 3. Advances in Pharmacogenomic-Guided Drug Development

### 3.1. Targeted Drug Therapy

With a high attrition rate in drug development, in which more than 90% of drugs fail during the process [72], 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 [73]. In 2013, the FDA issued industry guidance on clinical pharmacogenomics (PGx) and early-phase clinical studies [74]. 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 [75]. 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 [76].

### 3.2. 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 [76] [77]. 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 [78]. 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) [79] [80]. 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 [81]-[84].

### 3.3. 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 [85].

Important risk variables like inflammation, arterial calcification, and plasma lipoprotein levels are influenced by genetic differences, including mutations and frequent polymorphisms [86]. Heritability estimates for coronary atherosclerosis, which are based on fatal cardiac events, range from 38% to 57%, which is further supported by twin studies [87]. Genetic factors play crucial roles in many cardiovascular diseases, making them strong candidates for CRISPR-Cas9-based therapies. The heritability estimate for advanced atherosclerosis, the primary cause of coronary artery disease (CAD), ranges from 40% to 70%, indicating a significant genetic contribution to disease pathology [86].

Mutations in the LDLR gene are the main cause of familial hypercholesterolaemia (FH), the most common monogenic disorder linked to early cardiovascular disease (CVD), which affects approximately 1 in 200 people. Approximately 1000 pathogenic LDLR mutations out of more than 2900 have been detected. Similarly, mutations in more than 11 sarcomeric genes—of which more than 1400 variations have been found—are connected to hypertrophic cardiomyopathy (HCM), which affects 1 in 500 people [88]. Furthermore, the majority of arrhythmia syndromes are autosomally inherited, meaning that first-degree relatives have a 50% probability of experiencing the ailment [89]. A major risk factor for cardiovascular diseases, hypertension, is also significantly influenced by genetics. One of the most well-researched genes associated with blood pressure regulation is the AGT gene, which codes for angiotensinogen. Variations in AGT are associated with raised angiotensinogen levels and an increased risk of hypertension, highlighting the potential of genetic interventions in the treatment of this condition [90]. Heritability estimates for blood pressure range from 30% to 50%. Furthermore, cardiovascular complications like arrhythmias and cardiomyopathy affect about 40% of individuals with mitochondrial diseases; of these, cardiomyopathy is the most prevalent, affecting 20% - 25% of adults with mitochondrial disorders, while arrhythmias and conduction defects, like AV block and atrial fibrillation, occur in 26% of cases. This shows how mitochondrial genetic defects significantly contribute to the development of cardiovascular disease [91].

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 [92]. Furthermore, the development of CRISPR-Cas9 systems that rely on transitory pro-

tein 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 [93] 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 [94]. 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 [95]. Since low-density lipoprotein (LDL) is directly implicated in the development of atherosclerosis, 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) [96] [97]. 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 [98]-[100].

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 [101].

Outside of FH, CRISPR-Cas9 has been successfully used in genetic cardiomyopathies. Dilated cardiomyopathy (DCM), found in approximately one in every 250 people, is characterized as dilation of the ventricles, abnormal contractility, and high mortality [102]. 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 [103]. 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 [104].

CRISPR has also revealed viral cardiomyopathy mechanisms. Genome-wide screens identified ADAM9, a metalloproteinase necessary for EMCV infection, as a therapeutic target [105]. 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 [106] [107]. Some of the other examples include the correction of LZTR1 Noonan syndrome mutations [108], MYBPC3 embryonic mutation correction that is linked with HCM [109], and therapeutic PRKAG2 allele knockout in cardiac syndromes [110] [111]. In addition, AAV9-delivered CRISPR elimination of the RYR2 R176Q allele suppressed catecholaminergic polymorphic ventricular tachycardia (CPVT) [112], and PLN R14del mutation correction normalized calcium control and reduced arrhythmogenic risk [113].

Finally, CRISPR has been directed against Duchenne muscular dystrophy (DMD), a fatal X-linked illness defined by dystrophin deficiency [103]. 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.

### 3.4. 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 [114]. 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 [115]. 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 [116].

#### Clinical Uses, AI, and Drug Therapy for Cardiovascular Disease

AI's use in cardiovascular medicine has been a primary development in the field of cardiovascular medicine. The use of automated reasoning in correct medicine has markedly increased society genetics [117]. The synergies of artificial intelligence, enormous facts, and precision of medicine have been crucial for the creation of innovative medicines, helping to design productive treatments during the minimization of the risk of undesirable effects in humans. A number of CV medicines, including clopidogrel, warfarin, and lipid-lowering medicines, notably simvastatin, are currently being studied as curative targets [118].

Pharmacogenomics and precision medicine have already resulted in a significant discrepancy between the dose of warfarin and the various survival categories,

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 [119]. Similarly, Syn *et al.* produced comparable findings in a population of Asians taking warfarin. In addition, Li *et al.* used a backpropagation nervous system on the Web to predict the warfarin dose for patients who would undergo soul valve replacement [120]. Moreover, AI-enhanced deep learning structures are ready to revolutionize drug discovery, personalized drug therapy, and precision medicine.

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) [121]. 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.

Shah *et al.* reported three phenogroups associated with HFpEF. Phenogroup 1 (natriuretic peptide deficiency syndrome phenotype) is a young patient with fleshiness, few cardiac abnormalities, minimal brain natriuretic peptide (BNP) levels, and primarily beneficial effects [122]. Phenogroup 2 (obesity-cardiometabolic phenotype) was characterized by a high incidence of diabetes and corpulence, increased BNP tiers, and impaired left ventricular relaxation (defined by the last rate of vitamin E on echocardiography). Phenogroup 3 (cardierative phenotype) has a high incidence of electrocardiographic and echocardiographic abnormalities, together with kidney disease and a poor prognosis. Phenotyping of HFpEF patients could facilitate the development of targeted drug therapy and help in the design of upcoming clinical tests, which would indicate a patient's favorable response to detailed treatment [123]. Additionally, Przewlocka-Kosmala *et al.* [124] examined the relationship between exercise intolerance and ventricular systolic modesty function in HFpEF patients using machine learning. These findings suggest that poor modesty capacity is linked to lower left ventricular systolic function. There are still new opportunities for drug research and optimisation 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 optimisation are made possible in cardiovascular medicine by AI-driven algorithms that evaluate complicated datasets like imaging, genetic profiles, laboratory results, and electronic health records. AI and pharmacogenomics improve drug response prediction, reduce side effects, and direct individualised treatment. Models for allocating resources and preventing disease are further improved by cohort and population data. AI

helps with phenotyping, medication discovery, and clinical decision-making in real time in addition to diagnostics. Improved patient outcomes, cost effectiveness, and a shift towards individualised, predictive, and preventive cardiovascular care are all guaranteed by this smooth integration of AI into clinical operations.

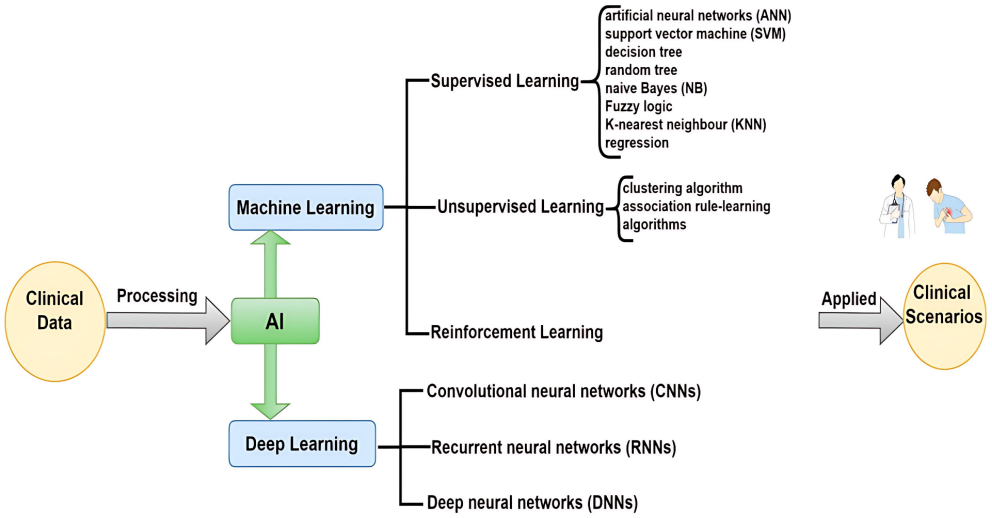


**Figure 1.** Application of AI in clinical practice [125].

**Table 2.** Artificial intelligence's use in cardiovascular research and medicine.

| Category | Examples of data/applications |
|---|---|
| Individual-specific data | Medical history, laboratory data, family history |
| Pharmacogenomics data | Drug-drug interactions, drug-gene interactions, population/individual data stratification |
| Cohort & population data | Medication data, environmental data, adverse effect profile, population genetics |
| AI/Machine learning role | Integration and analysis of heterogeneous data sources |
| Clinical applications | Phenotyping (phenomapping), pharmaceutical drug discovery, cardiovascular imaging, clinical practice |

## 4. 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.

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.

## 5. 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.

## Author Contribution Statement

**Ngabea Murtala Audu, Igbayilola Yusuff Dimeji, and Augustine Odili:** designed and conceptualized the research; conducted the investigations; analyzed and interpreted the data; contributed kits, equipment, and data analysis tools; and wrote the text.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## References

[1] Jørgensen, J.T. (2011) A Challenging Drug Development Process in the Era of Personalized Medicine. *Drug Discovery Today*, **16**, 891-897. https://doi.org/10.1016/j.drudis.2011.09.010

[2] US President's Council of Advisors on Science and Technology (PCAST) (2008) Priorities for Personalized Medicine. Executive Office of the President of the United States.

[3] Chan, I.S. and Ginsburg, G.S. (2011) Personalized Medicine: Progress and Promise. *Annual Review of Genomics and Human Genetics*, **12**, 217-244. https://doi.org/10.1146/annurev-genom-082410-101446

[4] Aneesh, T.P., Sonal Sekhar, M., Asha, A., Chandran, L. and Zachariah, S.M. (2009) Pharmacogenomics: The Right Drug to the Right Person. *Journal of Clinical Medicine Research*, **1**, 191-194. https://doi.org/10.4021/jocmr2009.08.1255

[5] Fiers, W., Contreras, R., Duerinck, F., Haegeman, G., Iserentant, D., Merregaert, J., *et al.* (1976) Complete Nucleotide Sequence of Bacteriophage MS2 RNA: Primary and Secondary Structure of the Replicase Gene. *Nature*, **260**, 500-507. https://doi.org/10.1038/260500a0

[6] Roden, D.M., McLeod, H.L., Relling, M.V., Williams, M.S., Mensah, G.A., Peterson, J.F., *et al.* (2019) Pharmacogenomics. *The Lancet*, **394**, 521-532. https://doi.org/10.1016/s0140-6736(19)31276-0

[7] Lu, A.Y. (1998) Drug-Metabolism Research Challenges in the New Millennium: Individual Variability in Drug Therapy and Drug Safety. *Drug Metabolism and Disposition*, **26**, 1217-1222.

[8] Roden, D.M., Van Driest, S.L., Wells, Q.S., Mosley, J.D., Denny, J.C. and Peterson, J.F. (2018) Opportunities and Challenges in Cardiovascular Pharmacogenomics: From Discovery to Implementation. *Circulation Research*, **122**, 1176-1190. https://doi.org/10.1161/circresaha.117.310965

[9] Zhou, Z. (2020) Pharmacogenomics in cardiovascular precision medicine. *Journal of Laboratory and Precision Medicine*, **5**, Article 30.

https://doi.org/10.21037/jlpm-2019-cpm-05

[10] Hodgson, J. and Marshall, A. (1998) Pharmacogenomics: Will the Regulators Approve? *Nature Biotechnology*, **16**, 243-246. https://doi.org/10.1038/nbt0398-243

[11] Hagihara, K., Kazui, M., Kurihara, A., Yoshiike, M., Honda, K., Okazaki, O., *et al.* (2009) A Possible Mechanism for the Differences in Efficiency and Variability of Active Metabolite Formation from Thienopyridine Antiplatelet Agents, Prasugrel and Clopidogrel. *Drug Metabolism and Disposition*, **37**, 2145-2152. https://doi.org/10.1124/dmd.109.028498

[12] Kazui, M., Nishiya, Y., Ishizuka, T., Hagihara, K., Farid, N.A., Okazaki, O., *et al.* (2010) Identification of the Human Cytochrome P450 Enzymes Involved in the Two Oxidative Steps in the Bioactivation of Clopidogrel to Its Pharmacologically Active Metabolite. *Drug Metabolism and Disposition*, **38**, 92-99. https://doi.org/10.1124/dmd.109.029132

[13] Sibbing, D., Koch, W., Gebhard, D., Schuster, T., Braun, S., Stegherr, J., *et al.* (2010) Cytochrome 2C19*17 Allelic Variant, Platelet Aggregation, Bleeding Events, and Stent Thrombosis in Clopidogrel-Treated Patients with Coronary Stent Placement. *Circulation*, **121**, 512-518. https://doi.org/10.1161/circulationaha.109.885194

[14] Lee, C.R., Luzum, J.A., Sangkuhl, K., Gammal, R.S., Sabatine, M.S., Stein, C.M., *et al.* (2022) Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. *Clinical Pharmacology & Therapeutics*, **112**, 959-967. https://doi.org/10.1002/cpt.2526

[15] Holmes, M.V., Perel, P., Shah, T., Hingorani, A.D. and Casas, J.P. (2011) CYP2C19 Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events: A Systematic Review and Meta-Analysis. *JAMA*, **306**, 2704-2714. https://doi.org/10.1001/jama.2011.1880

[16] Kayani, M., Sangeetha, G.K., Sarangi, S., Gaddamanugu, L.S., Sharma, S., Adedara, V.O., *et al.* (2025) Pharmacogenomics and Its Role in Cardiovascular Diseases: A Narrative Literature Review. *Current Cardiology Reviews*, **21**, e1573403X334668. https://doi.org/10.2174/011573403x334668241227074314

[17] Gennari, C., Nami, R., Pavese, G., Gragnani, S., Bianchini, C. and Buracchi, P. (1989) Calcium-Channel Blockade (Nitrendipine) in Combination with ACE Inhibition (Captopril) in the Treatment of Mild to Moderate Hypertension. *Cardiovascular Drugs and Therapy*, **3**, 319-325. https://doi.org/10.1007/bf00148477

[18] Todd, P.A. and Heel, R.C. (1986) Enalapril. A Review of Its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Use in Hypertension and Congestive Heart Failure. *Drugs*, **31**, 198-248. https://doi.org/10.2165/00003495-198631030-00002

[19] Messerli, F.H., Bangalore, S., Bavishi, C. and Rimoldi, S.F. (2018) Angiotensin-converting Enzyme Inhibitors in Hypertension. *Journal of the American College of Cardiology*, **71**, 1474-1482. https://doi.org/10.1016/j.jacc.2018.01.058

[20] James, P.A., Oparil, S., Carter, B.L., Cushman, W.C., Dennison-Himmelfarb, C., Handler, J., *et al.* (2014) 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). *JAMA*, **311**, 507-520. https://doi.org/10.1001/jama.2013.284427

[21] Rai, C.K., Kafle, R. and Makaju, S. (2022) Hypertension among Current Cigarette Smokers Visiting Outpatient Department of a Tertiary Care Centre: A Descriptive Cross-Sectional Study. *Journal of Nepal Medical Association*, **60**, 381-383.

https://doi.org/10.31729/jnma.7424

[22] Whelton, P.K., Carey, R.M., Aronow, W.S., Casey, D.E., Collins, K.J., *et al.* (2018) 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*, **71**, 1269-1324. https://doi.org/10.1161/hyp.0000000000000066

[23] Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M., *et al.* (2018) 2018 ESC/ESH Guidelines for the Management of Arterial Hypertension. *European Heart Journal*, **39**, 3021-3104. https://doi.org/10.1093/eurheartj/ehy339

[24] Seedat, Y.K. and Randeree, I.G.H. (1998) Antihypertensive Effect and Tolerability of Perindopril in Indian Hypertensive and Type 2 Diabetic Patients: 1-Year Randomised, Double-Blind, Parallel Study vs Atenolol. *Clinical Drug Investigation*, **16**, 229-240. https://doi.org/10.2165/00044011-199816030-00007

[25] Gavras, H., Faxon, D.P., Berkoben, J., Brunner, H.R. and Ryan, T.J. (1978) Angiotensin Converting Enzyme Inhibition in Patients with Congestive Heart Failure. *Circulation*, **58**, 770-776. https://doi.org/10.1161/01.cir.58.5.770

[26] Dzau, V.J., Colucci, W.S., Williams, G.H., Curfman, G., Meggs, L. and Hollenberg, N.K. (1980) Sustained Effectiveness of Converting-Enzyme Inhibition in Patients with Severe Congestive Heart Failure. *New England Journal of Medicine*, **302**, 1373-1379. https://doi.org/10.1056/nejm198006193022501

[27] CONSENSUS Trial Study Group (1987) Effects of Enalapril on Mortality in Severe Congestive Heart Failure. *New England Journal of Medicine*, **316**, 1429-1435. https://doi.org/10.1056/nejm198706043162301

[28] SOLVD Investigators, Yusuf, S., Pitt, B., Davis, C.E., Hood, W.B. and Cohn, J.N. (1991) Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure. *New England Journal of Medicine*, **325**, 293-302. https://doi.org/10.1056/nejm199108013250501

[29] Borghi, C., Omboni, S., Novo, S., Vinereanu, D., Ambrosio, G. and Ambrosioni, E. (2018) Efficacy and Safety of Zofenopril versus Ramipril in the Treatment of Myocardial Infarction and Heart Failure: A Review of the Published and Unpublished Data of the Randomized Double-Blind SMILE-4 Study. *Advances in Therapy*, **35**, 604-618. https://doi.org/10.1007/s12325-018-0697-x

[30] Pfeffer, M.A., Braunwald, E., Moyé, L.A., Basta, L., Brown, E.J., Cuddy, T.E., *et al.* (1992) Effect of Captopril on Mortality and Morbidity in Patients with Left Ventricular Dysfunction after Myocardial Infarction. *New England Journal of Medicine*, **327**, 669-677. https://doi.org/10.1056/nejm199209033271001

[31] Yancy, C.W., Jessup, M., Bozkurt, B., Butler, J., Casey, D.E., Colvin, M.M., *et al.* (2017) 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Journal of the American College of Cardiology*, **70**, 776-803. https://doi.org/10.1016/j.jacc.2017.04.025

[32] Ponikowski, P., Voors, A.A., Anker, S.D., Bueno, H., Cleland, J.G.F., Coats, A.J.S., *et al.* (2016) 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC)Developed with the Special Contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal*, **37**, 2129-2200. https://doi.org/10.1093/eurheartj/ehw128

[33] Folkow, B., Johansson, B. and Mellander, S. (1961) The Comparative Effects of Angiotensin and Noradrenaline on Consecutive Vascular Sections. *Acta Physiologica Scandinavica*, **53**, 99-104. https://doi.org/10.1111/j.1748-1716.1961.tb02267.x

[34] Kagami, S., Border, W.A., Miller, D.E. and Noble, N.A. (1994) Angiotensin II Stimulates Extracellular Matrix Protein Synthesis through Induction of Transforming Growth Factor-Beta Expression in Rat Glomerular Mesangial Cells. *Journal of Clinical Investigation*, **93**, 2431-2437. https://doi.org/10.1172/jci117251

[35] Berisha, B., Schams, D. and Miyamoto, A. (2002) The Expression of Angiotensin and Endothelin System Members in Bovine Corpus Luteum during Estrous Cycle and Pregnancy. *Endocrine*, **19**, 305-312. https://doi.org/10.1385/endo:19:3:305

[36] Andersson, R.G.G., Karlberg, B.E., Lindgren, B.R., Persson, K. and Rosenqvist, U. (1991) Enalaprilat, but Not Cilazaprilat, Increases Inflammatory Skin Reactions in Guinea-Pigs. *Drugs*, **41**, 48-53. https://doi.org/10.2165/00003495-199100411-00009

[37] Johnson, J.A., Gong, L., Whirl-Carrillo, M., Gage, B.F., Scott, S.A., Stein, C.M., *et al.* (2011) Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 Genotypes and Warfarin Dosing. *Clinical Pharmacology & Therapeutics*, **90**, 625-629. https://doi.org/10.1038/clpt.2011.185

[38] Bijl, M., Visser, L., van Schaik, R., Kors, J., Witteman, J., Hofman, A., *et al.* (2008) Genetic Variation in the CYP2D6 Gene Is Associated with a Lower Heart Rate and Blood Pressure in $\beta$-Blocker Users. *Clinical Pharmacology & Therapeutics*, **85**, 45-50. https://doi.org/10.1038/clpt.2008.172

[39] Cavallari, L.H. and Mason, D.L. (2016) Cardiovascular Pharmacogenomics—Implications for Patients with CKD. *Advances in Chronic Kidney Disease*, **23**, 82-90. https://doi.org/10.1053/j.ackd.2015.12.001

[40] Chen, L., Meyers, D., Javorsky, G., Burstow, D., Lolekha, P., Lucas, M., *et al.* (2007) Arg389Gly-$\beta$1-Adrenergic Receptors Determine Improvement in Left Ventricular Systolic Function in Nonischemic Cardiomyopathy Patients with Heart Failure after Chronic Treatment with Carvedilol. *Pharmacogenetics and Genomics*, **17**, 941-949. https://doi.org/10.1097/fpc.0b013e3282ef7354

[41] Vecchione, C., Villa, F., Carrizzo, A., Spinelli, C.C., Damato, A., Ambrosio, M., *et al.* (2017) A Rare Genetic Variant of BPIFB4 Predisposes to High Blood Pressure via Impairment of Nitric Oxide Signaling. *Scientific Reports*, **7**, Article No. 9706. https://doi.org/10.1038/s41598-017-10341-x

[42] Bristow, M.R., Murphy, G.A., Krause-Steinrauf, H., Anderson, J.L., Carlquist, J.F., Thaneemit-Chen, S., *et al.* (2010) An $\alpha_{2c}$-Adrenergic Receptor Polymorphism Alters the Norepinephrine-Lowering Effects and Therapeutic Response of the $\beta$-Blocker Bucindolol in Chronic Heart Failure. *Circulation: Heart Failure*, **3**, 21-28. https://doi.org/10.1161/circheartfailure.109.885962

[43] Lakkiss, B. and Refaat, M.M. (2023) $\beta_1$ and $\alpha_{2c}$-Adrenergic Receptor Polymorphisms Are Associated with Lower Incident Ventricular Fibrillation in Patients with ST-Segment-Elevation Myocardial Infarction. *Journal of the American Heart Association*, **12**, e029102. https://doi.org/10.1161/jaha.123.029102

[44] Troncoso, R., Moraga, F., Chiong, M., Roldán, J., Bravo, R., Valenzuela, R., *et al.* (2009) $Gln^{27}$→Glu$\beta_2$-Adrenergic Receptor Polymorphism in Heart Failure Patients: Differential Clinical and Oxidative Response to Carvedilol. *Basic & Clinical Pharmacology & Toxicology*, **104**, 374-378. https://doi.org/10.1111/j.1742-7843.2008.00370.x

[45] Qin, B., Yu, L., Wang, R., Tang, Y., Chen, Y., Wang, N., *et al.* (2023) Chemical Synthesis, Safety and Efficacy of Antihypertensive Candidate Drug 221s (2,9). *Molecules*, **28**, Article 4975. https://doi.org/10.3390/molecules28134975

[46] Green, S.A., Turki, J., Innis, M. and Liggett, S.B. (1994) Amino-Terminal Polymorphisms of the Human $\beta$2-Adrenergic Receptor Impart Distinct Agonist-Promoted Regulatory Properties. *Biochemistry*, **33**, 9414-9419. https://doi.org/10.1021/bi00198a006

[47] Yao, X., Xue, Y., Ma, Q., Bai, Y., Jia, P., Zhang, Y., *et al.* (2023) 221s-1a Inhibits Endothelial Proliferation in Pathological Angiogenesis through ERK/c-Myc Signaling. *European Journal of Pharmacology*, **952**, Article ID: 175805. https://doi.org/10.1016/j.ejphar.2023.175805

[48] Weeke, P. and Roden, D.M. (2013) Pharmacogenomics and Cardiovascular Disease. *Current Cardiology Reports*, **15**, Article No. 376. https://doi.org/10.1007/s11886-013-0376-0

[49] Castro-Moreno, P., Pardo, J.P., Hernández-Muñoz, R., López-Guerrero, J.J., Del Valle-Mondragón, L., Pastelín-Hernández, G., *et al.* (2012) Captopril Avoids Hypertension, the Increase in Plasma Angiotensiniibut Increases Angiotensin 1-7 and Angiotensinii-Induced Perfusion Pressure in Isolated Kidney in SHR. *Autonomic and Autacoid Pharmacology*, **32**, 61-69. https://doi.org/10.1111/aap.12001

[50] Petersen, M., Andersen, J.T., Hjelvang, B.R., Broedbaek, K., Afzal, S., Nyegaard, M., *et al.* (2011) Association of Beta-Adrenergic Receptor Polymorphisms and Mortality in Carvedilol-Treated Chronic Heart-Failure Patients. *British Journal of Clinical Pharmacology*, **71**, 556-565. https://doi.org/10.1111/j.1365-2125.2010.03868.x

[51] Chaturvedi, S., Lipszyc, D.H., Licht, C., Craig, J.C. and Parekh, R. (2014) Pharmacological Interventions for Hypertension in Children. *Evidence-Based Child Health: A Cochrane Review Journal*, **9**, 498-580. https://doi.org/10.1002/ebch.1974

[52] Jain, N., Nagaich, U., Pandey, M., Chellappan, D.K. and Dua, K. (2022) Predictive Genomic Tools in Disease Stratification and Targeted Prevention: A Recent Update in Personalized Therapy Advancements. *EPMA Journal*, **13**, 561-580. https://doi.org/10.1007/s13167-022-00304-2

[53] Mangravite, L.M., Thorn, C.F. and Krauss, R.M. (2006) Clinical Implications of Pharmacogenomics of Statin Treatment. *The Pharmacogenomics Journal*, **6**, 360-374. https://doi.org/10.1038/sj.tpj.6500384

[54] Tirona, R.G., Leake, B.F., Merino, G. and Kim, R.B. (2001) Polymorphisms in OATP-C: Identification of Multiple Allelic Variants Associated with Altered Transport Activity among European- and African-Americans. *Journal of Biological Chemistry*, **276**, 35669-35675. https://doi.org/10.1074/jbc.m103792200

[55] Niemi, M., Backman, J., Kajosaari, L., Leathart, J., Neuvonen, M., Daly, A., *et al.* (2005) Polymorphic Organic Anion Transporting Polypeptide 1B1 Is a Major Determinant of Repaglinide Pharmacokinetics. *Clinical Pharmacology & Therapeutics*, **77**, 468-478. https://doi.org/10.1016/j.clpt.2005.01.018

[56] Igel, M., Arnold, K., Niemi, M., Hofmann, U., Schwab, M., Lutjohann, D., *et al.* (2006) Impact of the SLCO1B1 Polymorphism on the Pharmacokinetics and Lipid-Lowering Efficacy of Multiple-Dose Pravastatin. *Clinical Pharmacology & Therapeutics*, **79**, 419-426. https://doi.org/10.1016/j.clpt.2006.01.010

[57] SEARCH Collaborative Group, Link, E., Parish, S., Armitage, J., Bowman, L., Heath, S., Matsuda, F., Gut, I., Lathrop, M. and Collins, R. (2008) SLCO1B1 Variants and Statin-Induced Myopathy—A Genomewide Study. *The New England Journal of Medicine*, **359**, 789-799. https://doi.org/10.1056/NEJMoa0801936

[58] Voora, D., Shah, S.H., Spasojevic, I., Ali, S., Reed, C.R., Salisbury, B.A., *et al.* (2009) The SLCO1B1*5 Genetic Variant Is Associated with Statin-Induced Side Effects.

*Journal of the American College of Cardiology*, **54**, 1609-1616. https://doi.org/10.1016/j.jacc.2009.04.053

[59] Donnelly, L.A., Doney, A.S.F., Tavendale, R., Lang, C.C., Pearson, E.R., Colhoun, H.M., *et al.* (2010) Common Nonsynonymous Substitutions in SLCO1B1 Predispose to Statin Intolerance in Routinely Treated Individuals with Type 2 Diabetes: A Go-Darts Study. *Clinical Pharmacology & Therapeutics*, **89**, 210-216. https://doi.org/10.1038/clpt.2010.255

[60] Voora, D. and Ginsburg, G.S. (2012) Clinical Application of Cardiovascular Pharmacogenetics. *Journal of the American College of Cardiology*, **60**, 9-20. https://doi.org/10.1016/j.jacc.2012.01.067

[61] Donnelly, L.A., Doney, A.S.F., Dannfald, J., Whitley, A.L., Lang, C.C., Morris, A.D., *et al.* (2008) A Paucimorphic Variant in the HMG-CoA Reductase Gene Is Associated with Lipid-Lowering Response to Statin Treatment in Diabetes: A GoDARTS Study. *Pharmacogenetics and Genomics*, **18**, 1021-1026. https://doi.org/10.1097/fpc.0b013e3283106071

[62] Thompson, J.F., Hyde, C.L., Wood, L.S., Paciga, S.A., Hinds, D.A., Cox, D.R., *et al.* (2009) Comprehensive Whole-Genome and Candidate Gene Analysis for Response to Statin Therapy in the Treating to New Targets (TNT) Cohort. *Circulation*: *Cardiovascular Genetics*, **2**, 173-181. https://doi.org/10.1161/circgenetics.108.818062

[63] Zintzaras, E., Kitsios, G.D., Triposkiadis, F., Lau, J. and Raman, G. (2009) APOE Gene Polymorphisms and Response to Statin Therapy. *The Pharmacogenomics Journal*, **9**, 248-257. https://doi.org/10.1038/tpj.2009.25

[64] Li, Y., Iakoubova, O.A., Shiffman, D., Devlin, J.J., Forrester, J.S. and Superko, H.R. (2010) KIF6 Polymorphism as a Predictor of Risk of Coronary Events and of Clinical Event Reduction by Statin Therapy. *The American Journal of Cardiology*, **106**, 994-998. https://doi.org/10.1016/j.amjcard.2010.05.033

[65] Iakoubova, O.A., Robertson, M., Tong, C.H., Rowland, C.M., Catanese, J.J., Blauw, G.J., *et al.* (2010) KIF6 Trp719Arg Polymorphism and the Effect of Statin Therapy in Elderly Patients: Results from the PROSPER Study. *European Journal of Cardiovascular Prevention & Rehabilitation*, **17**, 455-461. https://doi.org/10.1097/hjr.0b013e328336a0dd

[66] Sainz de Medrano Sainz, J.I. and Brunet Serra, M. (2023) Influence of Pharmacogenetics on the Diversity of Response to Statins Associated with Adverse Drug Reactions. *Advances in Laboratory Medicine/Avances en Medicina de Laboratorio*, **4**, 341-352. https://doi.org/10.1515/almed-2023-0123

[67] Tomlinson, B., Hu, M., Lee, V.W.Y., Lui, S.S.H., Chu, T.T.W., Poon, E.W.M., *et al.* (2010) ABCG2 Polymorphism Is Associated with the Low-Density Lipoprotein Cholesterol Response to Rosuvastatin. *Clinical Pharmacology & Therapeutics*, **87**, 558-562. https://doi.org/10.1038/clpt.2009.232

[68] Mangravite, L.M., Medina, M.W., Cui, J., Pressman, S., Smith, J.D., Rieder, M.J., *et al.* (2010) Combined Influence of *LDLR* and *HMGCR* Sequence Variation on Lipid-Lowering Response to Simvastatin. *Arteriosclerosis*, *Thrombosis*, *and Vascular Biology*, **30**, 1485-1492. https://doi.org/10.1161/atvbaha.110.203273

[69] Barber, M.J., Mangravite, L.M., Hyde, C.L., Chasman, D.I., Smith, J.D., McCarty, C.A., *et al.* (2010) Genome-Wide Association of Lipid-Lowering Response to Statins in Combined Study Populations. *PLOS ONE*, **5**, e9763. https://doi.org/10.1371/journal.pone.0009763

[70] Xu, M., Zhang, K. and Song, J. (2021) Targeted Therapy in Cardiovascular Disease: A Precision Therapy Era. *Frontiers in Pharmacology*, **12**, Article 623674.

https://doi.org/10.3389/fphar.2021.623674

[71] Li, X., Wang, Z., Chen, W., Wei, C., Lu, W., Zhou, R., *et al.* (2025) Construction and Validation of a Machine Learning Model to Predict the Risk of Nasopharyngeal Carcinoma Using Multimodal Clinical Data: A Single-Center, Retrospective Study. *Clinical and Translational Oncology*. https://doi.org/10.1007/s12094-025-03992-0

[72] Abad-Santos, F., Aliño, S.F., Borobia, A.M., García-Martín, E., Gassó, P., Maroñas, O., *et al.* (2024) Developments in Pharmacogenetics, Pharmacogenomics, and Personalized Medicine. *Pharmacological Research*, **200**, Article ID: 107061. https://doi.org/10.1016/j.phrs.2024.107061

[73] Gulilat, M., Lamb, T., Teft, W.A., Wang, J., Dron, J.S., Robinson, J.F., *et al.* (2019) Targeted Next Generation Sequencing as a Tool for Precision Medicine. *BMC Medical Genomics*, **12**, Article No. 81. https://doi.org/10.1186/s12920-019-0527-2

[74] Kim, Y., Landstrom, A.P., Shah, S.H., Wu, J.C. and Seidman, C.E. (2024) Gene Therapy in Cardiovascular Disease: Recent Advances and Future Directions in Science: A Science Advisory from the American Heart Association. *Circulation*, **150**, e471-e480. https://doi.org/10.1161/cir.0000000000001296

[75] Collins, F.S., Morgan, M. and Patrinos, A. (2003) The Human Genome Project: Lessons from Large-Scale Biology. *Science*, **300**, 286-290. https://doi.org/10.1126/science.1084564

[76] Schuster, S.C. (2007) Next-Generation Sequencing Transforms Today's Biology. *Nature Methods*, **5**, 16-18. https://doi.org/10.1038/nmeth1156

[77] Yadav, D., Patil-Takbhate, B., Khandagale, A., Bhawalkar, J., Tripathy, S. and Khopkar-Kale, P. (2023) Next-Generation Sequencing Transforming Clinical Practice and Precision Medicine. *Clinica Chimica Acta*, **551**, Article ID: 117568. https://doi.org/10.1016/j.cca.2023.117568

[78] Zehir, A., Benayed, R., Shah, R.H., Syed, A., Middha, S., Kim, H.R., *et al.* (2017) Erratum: Mutational Landscape of Metastatic Cancer Revealed from Prospective Clinical Sequencing of 10,000 Patients. *Nature Medicine*, **23**, 1004-1004. https://doi.org/10.1038/nm0817-1004c

[79] Antman, E.M. and Loscalzo, J. (2016) Precision Medicine in Cardiology. *Nature Reviews Cardiology*, **13**, 591-602. https://doi.org/10.1038/nrcardio.2016.101

[80] Ashina, M., Terwindt, G.M., Al-Karagholi, M.A., de Boer, I., Lee, M.J., Hay, D.L., *et al.* (2021) Migraine: Disease Characterisation, Biomarkers, and Precision Medicine. *The Lancet*, **397**, 1496-1504. https://doi.org/10.1016/s0140-6736(20)32162-0

[81] Brown, K.D., Campbell, C. and Roberts, G.V. (2020) Precision Medicine in Kidney Disease: The Patient's View. *Nature Reviews Nephrology*, **16**, 625-627. https://doi.org/10.1038/s41581-020-0319-0

[82] Chung, W.K., Erion, K., Florez, J.C., Hattersley, A.T., Hivert, M., Lee, C.G., *et al.* (2020) Precision Medicine in Diabetes: A Consensus Report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*, **63**, 1671-1693. https://doi.org/10.1007/s00125-020-05181-w

[83] Zheng, R., Zhang, L., Parvin, R., Su, L., Chi, J., Shi, K., *et al.* (2023) Progress and Perspective of CRISPR-Cas9 Technology in Translational Medicine. *Advanced Science*, **10**, Article ID: 2300195. https://doi.org/10.1002/advs.202300195

[84] Aherrahrou, R., Guo, L., Nagraj, V.P., Aguhob, A., Hinkle, J., Chen, L., *et al.* (2020) Genetic Regulation of Atherosclerosis-Relevant Phenotypes in Human Vascular Smooth Muscle Cells. *Circulation Research*, **127**, 1552-1565. https://doi.org/10.1161/circresaha.120.317415

[85] Biros, E., Karan, M. and Golledge, J. (2008) Genetic Variation and Atherosclerosis. *Current Genomics*, **9**, 29-42. https://doi.org/10.2174/138920208783884856

[86] Vrablik, M., Dlouha, D., Todorovova, V., Stefler, D. and Hubacek, J.A. (2021) Genetics of Cardiovascular Disease: How Far Are We from Personalized CVD Risk Prediction and Management? *International Journal of Molecular Sciences*, **22**, Article 4182. https://doi.org/10.3390/ijms22084182

[87] Gray, B. and Behr, E.R. (2016) New Insights into the Genetic Basis of Inherited Arrhythmia Syndromes. *Circulation*: *Cardiovascular Genetics*, **9**, 569-577. https://doi.org/10.1161/circgenetics.116.001571

[88] Franceschini, N. and Le, T.H. (2014) Genetics of Hypertension: Discoveries from the Bench to Human Populations. *American Journal of Physiology-Renal Physiology*, **306**, F1-F11. https://doi.org/10.1152/ajprenal.00334.2013

[89] Bray, A.W. and Ballinger, S.W. (2017) Mitochondrial DNA Mutations and Cardiovascular Disease. *Current Opinion in Cardiology*, **32**, 267-274. https://doi.org/10.1097/hco.0000000000000383

[90] German, D.M., Mitalipov, S., Mishra, A. and Kaul, S. (2019) Therapeutic Genome Editing in Cardiovascular Diseases. *JACC*: *Basic to Translational Science*, **4**, 122-131. https://doi.org/10.1016/j.jacbts.2018.11.004

[91] WHO (2024) The Top 10 Causes of Death. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

[92] He, Z., Luo, J., Lv, M., Li, Q., Ke, W., Niu, X., *et al.* (2023) Characteristics and Evaluation of Atherosclerotic Plaques: An Overview of State-Of-The-Art Techniques. *Frontiers in Neurology*, **14**, Article 1159288. https://doi.org/10.3389/fneur.2023.1159288

[93] Zhao, H., Li, Y., He, L., Pu, W., Yu, W., Li, Y., *et al.* (2020) *In Vivo* AAV-CRISPR/Cas9-Mediated Gene Editing Ameliorates Atherosclerosis in Familial Hypercholesterolemia. *Circulation*, **141**, 67-79. https://doi.org/10.1161/circulationaha.119.042476

[94] Hershberger, R.E., Hedges, D.J. and Morales, A. (2013) Dilated Cardiomyopathy: The Complexity of a Diverse Genetic Architecture. *Nature Reviews Cardiology*, **10**, 531-547. https://doi.org/10.1038/nrcardio.2013.105

[95] Nishiyama, T., Zhang, Y., Cui, M., Li, H., Sanchez-Ortiz, E., McAnally, J.R., *et al.* (2022) Precise Genomic Editing of Pathogenic Mutations in *RBM*20 Rescues Dilated Cardiomyopathy. *Science Translational Medicine*, **14**, eade1633. https://doi.org/10.1126/scitranslmed.ade1633

[96] Fomin, A., Gärtner, A., Cyganek, L., Tiburcy, M., Tuleta, I., Wellers, L., *et al.* (2021) Truncated Titin Proteins and Titin Haploinsufficiency Are Targets for Functional Recovery in Human Cardiomyopathy Due to *TTN* Mutations. *Science Translational Medicine*, **13**, eabd3079. https://doi.org/10.1126/scitranslmed.abd3079

[97] Bazzone, L.E., King, M., MacKay, C.R., Kyawe, P.P., Meraner, P., Lindstrom, D., *et al.* (2019) A Disintegrin and Metalloproteinase 9 Domain (ADAM9) Is a Major Susceptibility Factor in the Early Stages of Encephalomyocarditis Virus Infection. *mBio*, **10**, e02734-18. https://doi.org/10.1128/mbio.02734-18

[98] Carroll, K.J., Makarewich, C.A., McAnally, J., Anderson, D.M., Zentilin, L., Liu, N., *et al.* (2015) A Mouse Model for Adult Cardiac-Specific Gene Deletion with CRISPR/Cas9. *Proceedings of the National Academy of Sciences of the United States of America*, **113**, 338-343. https://doi.org/10.1073/pnas.1523918113

[99] Kyriakopoulou, E., Monnikhof, T. and van Rooij, E. (2023) Gene Editing Innovations

and Their Applications in Cardiomyopathy Research. *Disease Models & Mechanisms*, **16**, dmm050088. https://doi.org/10.1242/dmm.050088

[100] Hanses, U., Kleinsorge, M., Roos, L., Yigit, G., Li, Y., Barbarics, B., *et al.* (2020) Intronic CRISPR Repair in a Preclinical Model of Noonan Syndrome-Associated Cardiomyopathy. *Circulation*, **142**, 1059-1076. https://doi.org/10.1161/circulationaha.119.044794

[101] Hu, D., Hu, D., Liu, L., Barr, D., Liu, Y., Balderrabano-Saucedo, N., *et al.* (2020) Identification, Clinical Manifestation and Structural Mechanisms of Mutations in AMPK Associated Cardiac Glycogen Storage Disease. *EBioMedicine*, **54**, Article ID: 102723. https://doi.org/10.1016/j.ebiom.2020.102723

[102] Xie, C., Zhang, Y., Song, L., Luo, J., Qi, W., Hu, J., *et al.* (2016) Genome Editing with CRISPR/Cas9 in Postnatal Mice Corrects PRKAG2 Cardiac Syndrome. *Cell Research*, **26**, 1099-1111. https://doi.org/10.1038/cr.2016.101

[103] Pan, X., Philippen, L., Lahiri, S.K., Lee, C., Park, S.H., Word, T.A., *et al.* (2018) *In Vivo RYR*2 Editing Corrects Catecholaminergic Polymorphic Ventricular Tachycardia. *Circulation Research*, **123**, 953-963. https://doi.org/10.1161/circresaha.118.313369

[104] Dave, J., Raad, N., Mittal, N., Zhang, L., Fargnoli, A., Oh, J.G., *et al.* (2022) Gene Editing Reverses Arrhythmia Susceptibility in Humanized PLN-R14del Mice: Modelling a European Cardiomyopathy with Global Impact. *Cardiovascular Research*, **118**, 3140-3150. https://doi.org/10.1093/cvr/cvac021

[105] Bushby, K., Finkel, R., Birnkrant, D.J., Case, L.E., Clemens, P.R., Cripe, L., *et al.* (2010) Diagnosis and Management of Duchenne Muscular Dystrophy, Part 1: Diagnosis, and Pharmacological and Psychosocial Management. *The Lancet Neurology*, **9**, 77-93. https://doi.org/10.1016/s1474-4422(09)70271-6

[106] Fayssoil, A., Nardi, O., Orlikowski, D. and Annane, D. (2009) Cardiomyopathy in Duchenne Muscular Dystrophy: Pathogenesis and Therapeutics. *Heart Failure Reviews*, **15**, 103-107. https://doi.org/10.1007/s10741-009-9156-8

[107] Li, J., Wang, K., Zhang, Y., Qi, T., Yuan, J., Zhang, L., *et al.* (2021) Therapeutic Exon Skipping through a CRISPR-Guided Cytidine Deaminase Rescues Dystrophic Cardiomyopathy *in Vivo*. *Circulation*, **144**, 1760-1776. https://doi.org/10.1161/circulationaha.121.054628

[108] Min, Y., Li, H., Rodriguez-Caycedo, C., Mireault, A.A., Huang, J., Shelton, J.M., *et al.* (2019) CRISPR-Cas9 Corrects Duchenne Muscular Dystrophy Exon 44 Deletion Mutations in Mice and Human Cells. *Science Advances*, **5**, eaav4324. https://doi.org/10.1126/sciadv.aav4324

[109] Singh, D.B. (2019) The Impact of Pharmacogenomics in Personalized Medicine. In: Silva, A.C., Moreira, J.N., Lobo, J.M.S. and Almeida, H., Eds., *Current Applications of Pharmaceutical Biotechnology*, Springer, 369-394. https://doi.org/10.1007/10_2019_110

[110] Naik, K., Goyal, R.K., Foschini, L., Chak, C.W., Thielscher, C., Zhu, H., *et al.* (2024) Current Status and Future Directions: The Application of Artificial Intelligence/Machine Learning for Precision Medicine. *Clinical Pharmacology & Therapeutics*, **115**, 673-686. https://doi.org/10.1002/cpt.3152

[111] Cavallari, L.H. and Weitzel, K. (2015) Pharmacogenomics in Cardiology—Genetics and Drug Response: 10 Years of Progress. *Future Cardiology*, **11**, 281-286. https://doi.org/10.2217/fca.15.20

[112] Sibbing, D., Aradi, D., Alexopoulos, D., ten Berg, J., Bhatt, D.L., Bonello, L., *et al.*

(2019) Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding P2Y12 Receptor Inhibitor Treatment in Percutaneous Coronary Intervention. *JACC*: *Cardiovascular Interventions*, **12**, 1521-1537. https://doi.org/10.1016/j.jcin.2019.03.034

[113] Kitzmiller, J., Mikulik, E., Dauki, A., Mukherjee, C. and Luzum, J. (2016) Pharmacogenomics of Statins: Understanding Susceptibility to Adverse Effects. *Pharmacogenomics and Personalized Medicine*, **9**, 97-106. https://doi.org/10.2147/pgpm.s86013

[114] Bonowicz, K., Jerka, D., Piekarska, K., Olagbaju, J., Stapleton, L., Shobowale, M., *et al.* (2025) CRISPR-Cas9 in Cardiovascular Medicine: Unlocking New Potential for Treatment. *Cells*, **14**, Article 131. https://doi.org/10.3390/cells14020131

[115] Deiman, F.E., Bomer, N., van der Meer, P. and Grote Beverborg, N. (2022) Review: Precision Medicine Approaches for Genetic Cardiomyopathy: Targeting Phospholamban R14del. *Current Heart Failure Reports*, **19**, 170-179. https://doi.org/10.1007/s11897-022-00558-x

[116] Min, Y., Bassel-Duby, R. and Olson, E.N. (2019) CRISPR Correction of Duchenne Muscular Dystrophy. *Annual Review of Medicine*, **70**, 239-255. https://doi.org/10.1146/annurev-med-081117-010451

[117] Zhu, P., Wu, F., Mosenson, J., Zhang, H., He, T. and Wu, W. (2017) CRISPR/Cas9-Mediated Genome Editing Corrects Dystrophin Mutation in Skeletal Muscle Stem Cells in a Mouse Model of Muscle Dystrophy. *Molecular Therapy—Nucleic Acids*, **7**, 31-41. https://doi.org/10.1016/j.omtn.2017.02.007

[118] Ali, A., Rahman, M.Y. and Sheikh, D. (2024) The Role of CRISPR/Cas9 in Revolutionizing Duchenne's Muscular Dystrophy Treatment: Opportunities and Obstacles. *Global Medical Genetics*, **11**, 349-357. https://doi.org/10.1055/s-0044-1791803

[119] Pirmohamed, M., Burnside, G., Eriksson, N., Jorgensen, A.L., Toh, C.H., Nicholson, T., *et al.* (2013) A Randomized Trial of Genotype-Guided Dosing of Warfarin. *New England Journal of Medicine*, **369**, 2294-2303. https://doi.org/10.1056/nejmoa1311386

[120] Syn, N.L., Wong, A.L., Lee, S., Teoh, H., Yip, J.W.L., Seet, R.C., *et al.* (2018) Genotype-Guided versus Traditional Clinical Dosing of Warfarin in Patients of Asian Ancestry: A Randomized Controlled Trial. *BMC Medicine*, **16**, Article No. 104. https://doi.org/10.1186/s12916-018-1093-8

[121] Li, Q., Wang, J., Tao, H., Zhou, Q., Chen, J., Fu, B., *et al.* (2019) The Prediction Model of Warfarin Individual Maintenance Dose for Patients Undergoing Heart Valve Replacement, Based on the Back Propagation Neural Network. *Clinical Drug Investigation*, **40**, 41-53. https://doi.org/10.1007/s40261-019-00850-0

[122] Shah, S.J., Katz, D.H., Selvaraj, S., Burke, M.A., Yancy, C.W., Gheorghiade, M., *et al.* (2015) Phenomapping for Novel Classification of Heart Failure with Preserved Ejection Fraction. *Circulation*, **131**, 269-279. https://doi.org/10.1161/circulationaha.114.010637

[123] Shah, S.J. (2017) Precision Medicine for Heart Failure with Preserved Ejection Fraction: An Overview. *Journal of Cardiovascular Translational Research*, **10**, 233-244. https://doi.org/10.1007/s12265-017-9756-y

[124] Przewlocka-Kosmala, M., Marwick, T.H., Dabrowski, A. and Kosmala, W. (2019) Contribution of Cardiovascular Reserve to Prognostic Categories of Heart Failure with Preserved Ejection Fraction: A Classification Based on Machine Learning. *Journal of the American Society of Echocardiography*, **32**, 604-615.e6. https://doi.org/10.1016/j.echo.2018.12.002

[125] Khan, M.R., Haider, Z.M., Hussain, J., Malik, F.H., Talib, I. and Abdullah, S. (2024) Comprehensive Analysis of Cardiovascular Diseases: Symptoms, Diagnosis, and AI Innovations. *Bioengineering*, **11**, Article 1239. https://doi.org/10.3390/bioengineering11121239