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PHARMACOGENOMICS IN CARDIOVASCULAR DISEASES - A PATH TO PERSONALISED MEDICINE

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ABSTRACT

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, posing a major challenge to global health systems. Despite significant advances in therapeutics, variability in drug response continues to limit treatment efficacy and safety. Pharmacogenomics—the study of how genetic variations influence drug metabolism, efficacy, and toxicity—offers a transformative approach to optimizing cardiovascular therapy. By identifying genetic determinants that affect drug targets, transporters, and metabolizing enzymes, pharmacogenomics enables clinicians to tailor treatment strategies to individual genetic profiles. Key examples include genotype-guided dosing of warfarin (CYP2C9, VKORC1), clopidogrel responsiveness (CYP2C19), and statin-induced myopathy risk (SLCO1B1). Integrating pharmacogenomic testing into clinical practice can enhance therapeutic precision, reduce adverse drug reactions, and improve patient outcomes. However, challenges such as cost, limited clinical implementation, and lack of diverse population data remain barriers to widespread adoption. As genomic technologies advance and evidence-based guidelines evolve, pharmacogenomics represents a critical step toward realizing the promise of personalized medicine in cardiovascular care.

KEYWORDS: pharmacogenomics, cardiovascular diseases, personalized medicine, genetic variation, drug response, precision therapy.

INTRODUCTION

Pharmacogenomics (also known as pharmacogenetics) is the study of how our genes affect the way we respond to medications. The word "pharmacogenomics" comes from the words "pharmacology" (the study of the uses and effects of medications) and "genomics" (the study of genes and their functions).[1]

The term Pharmacogenetics was first coined by Friedrich Vogel in 1959.In the late 1990s, with advancements in DNA technology and genomic sciences, pharmacogenomics a newer term was introduced.[2] Pharmacogenomics is part of the field of precision medicine.

Pharmacogenomics can help your healthcare provider prescribe a medication that leads to fewer side effects or that may work better for you.[1] Substantial progress has been made over the past decade in improving our understanding of genetic determinants influencing response to cardiovascular drugs.

These advances have fueled a hope for "personalized medicine" which includes tailoring of diagnostic and treatment strategies to the needs and characteristics of individual patients – including genomic variation as well as other features such as personal preferences or access to care – aiming to improve drug responsiveness and lessen risk of toxicity.[3] As our knowledge of genetics increases we are moving more towards a time where medicine can be individualized to the patient. By using a person's individual genetics we are provided with information that will allow us to select a medication with the best chance of efficacy, the best dose, and the lowest likelihood of serious side effects. It has long been understood that medications will have variable effects on an individual basis.[4]

HISTORY OF PHARMACOGENOMICS

The history of pharmacogenetics can be traced to Pythagoras, the Greek mathematician and philosopher, who described life threatening haemolysis in people eating the broad bean Vicia faba, which was and remains a basic essential food in many Mediterranean countries. The haemolysis was subsequently shown to be associated with glucose-6-phosphate dehydrogenase deficiency(G6PD), which is probably the most common enzymatic deficiency in the world with over a half a billion people affected. G6PD shows large inter ethnic differences in the frequency of its geno and phenotypes, and with a very large number of gene mutations.

In the late 1930's the first experimental pharmacogenetic study was conducted in which subjects were tested for their taste, sensitivity(bitterness) to PTC(phenylthiocarbamide). Large ethnic differences in the phenotype were found (non-tasters frequency: 30% Caucasians, 9% African Americans)and the mode of inheritance was elucidated. This work is considered to be the first controlled study of a common human genetic polymorphism in response to a chemical. In the 1950s, three landmark discoveries were made: a) the finding that the primaquine induced acute haemolytic crises, that occurred during World War II in the Pacific arena was caused by the G6PD deficiency b) the mechanism for the prolonged apnea to succinylcholine was discovered by Kalow as a pseudocholinesterase deficiency c) the acetylation polymorphism of isoniazid with subjects classified as fast and slow acetylators and the link of slow acetylation to isoniazid-induced peripheral neuropathy. The 1960's were rather a dormant period for pharmacogenetics. Nevertheless, Kalow produced the first monograph on pharmacogenetics.

In the 1970's, two back-to-back presentations at the 6th IUPHAR Congress in Helsinki described adverse effects in subjects due to their inability to oxidatively metabolise the drugs sparteine and debrisoquine. In the 1980's, the

CYP2D6 enzyme was purified, Poor metabolizers were shown to have no CYP2D6 protein, its gene was cloned, mutant alleles detected, and Meyer and colleagues described the first allele-specific PCR reaction. In the 1990's, many other genetic polymorphisms of CYPs were identified that had major pharmacokinetic impact (e.g.CYP2C19, CYP2C9, CYP2B6), the NAT2 polymorphism was discovered and the molecular basis for the TPMT(thiopurine methyltransferase) deficiency was elucidated by Weinshilboum. The first journal with the title of pharmacogenetics was published and the term pharmacogenomics was coined but this led to a large number of often confusing definitions.[5]

The Human Genome Project, which sequenced the first whole genome in 2001, altered many aspects of genetics and accelerated the rate of pharmacogenetics discovery The draft genome for dogs and cats was published in 2005 and 2007, respectively whereas genome sequences of domestic cattle (Bos taurus) and horses were released in 2009. The discovery of these sequences was accompanied by the development of a broader set of tools for querying the generated data, which aided in the advancement of the field of pharmacogenomics.[6]

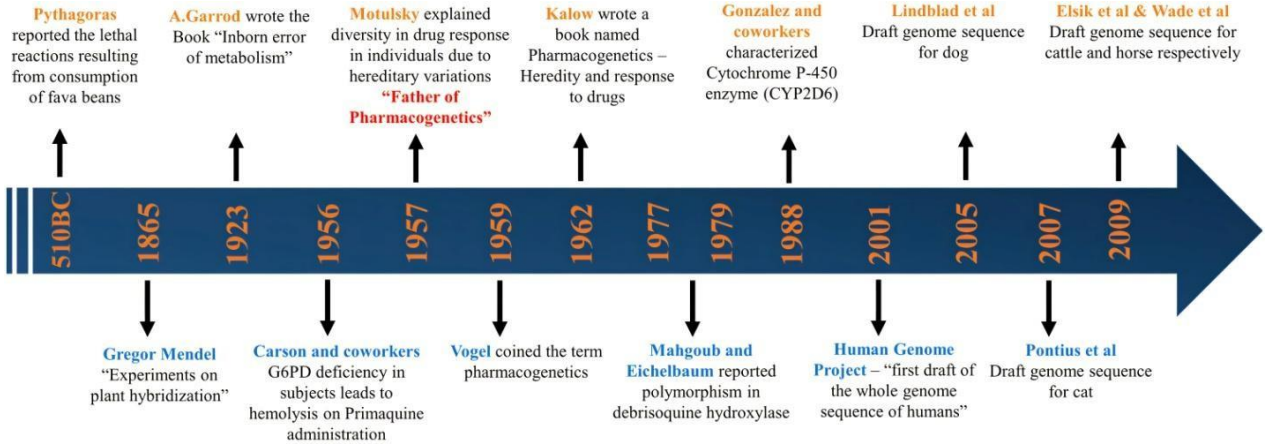

Figure 1: Major Historical landmarks of Pharmacogenetics.[6]

OVERVIEW OF PHARMACOGENOMICS IN CVS THERAPY

Pharmacogenetics can improve clinical outcomes by reducing adverse drug effects and enhancing therapeutic efficacy for commonly used drugs that treat a wide range of cardiovascular diseases. One of the major barriers to the clinical implementation of cardiovascular pharmacogenetics is limited education on this field for current healthcare providers and students. The abundance of pharmacogenetic literature underscores its promise, but it can also be challenging to learn such a wealth of information. To date, clinical implementation of pharmacogenetics in the cardiovascular domain has largely centered around three drugs/therapeutic classes: clopidogrel, warfarin, and statins.[7]

However, several other drugs and drug classes may soon join their ranks. The more desirable model of pharmacogenomics testing is the preemptive approach that has genotyping performed before the patient receives drug prescription and dosage. Although this model actually improves the efficiency of genotyping and prepares the patient to have information ready at future occasions of medication selection and dosing.

In the field of cardiovascular medicine, the most prevalent pharmacogenomics testing are warfarin and cytochrome P450 family 2 subfamily C member 9 (CYP2C9)/vitamin K epOxide reductase complex subunit 1 (VKORC1) genotypes, clopidogrel and CYP2C19 genotype, and simvastatin and solute carrier organic anion transporter family

member 1B1 (SLCO1B1) genotype. CPIC guidelines are available for each of these drug-gene pairs, and a number of institutions including our own are implementing these into clinical practice.[8]

WHY PERSONALISATION MATTERS IN CVS THERAPY?

In the late 1990s, the term 'personalized medicine' was first introduced after its scientific basis had been set over the preceding decades. The Council of Advisors on Science and Technology of USA defined that "Personalized medicine refers to the tailoring of medical treatment to the individual characteristics of each patient".[9] One of the key aspects of this movement away from one-size-fits-all patient management is the selection and dosage of medications. Human body's response to drug is mainly determined by two variable process, pharmacokinetics and pharmacodynamics. Pharmacokinetics describes the time course of drug concentration change during which drugs are deposited and cleared in body compartments through absorption, distribution, metabolism, and excretion. Pharmacodynamics refers to drug actions at a constant concentration including interaction with receptors, target cells and downstream signaling.[8]

Individualized medicine serves a pivotal role in the evolution of national and global healthcare reform, especially, in the CVDs fields. There may be many benefits of personalized medicine; making better medication choices (100000 Americans die from adverse reactions to medications); select optimal therapy (on average, only 50% of people respond, 30% in hypertension ; safer dosing options (one size does not fix all); improvements in drug development (focused drug testing); decrease health care costs; decrease ADRs (Avoiding ADRs the fourth leading of cause of death according to FDA); potential to improve patient safety; reduce inappropriate testing and procedures; increased patient empowerment and awareness.

In the era of genomics, personalized medicine combines the genetic information for additional benefit in preventive and therapeutic strategies. Personalized medicine may allow the physician to provide a better therapy for patients in terms of efficiency, safety and treatment length to reduce the associated costs. There was a remarkable growth in scientific publication on personalized medicine within the past few years in the cardiovascular field. In medical practice, it is important to treat not only the disease, but also the patient, who by all accounts should be included in the decision-making process psycho-socio-economically.[9]

CARDIOVASCULAR DISEASES AND STANDARD THERAPIES

- **Common Types of CVD'S**

The most common types of cardiovascular disease include:

1. **Arrhythmia:** Occurs when the heart beats too fast or irregularly which can cause heart palpitations, dizziness, and fainting.
2. **Coronary Artery Disease (CAD):** Occurs when the arteries that supply blood to the heart narrow or become blocked, which can lead to chest pain or a Heart attack
3. **Heart Failure:** Occurs when the heart is unable to pump enough blood to meet the body's needs and can cause fatigue and breathlessness.
4. **Peripheral Arterial Disease (PAD):** Occurs when the arteries that supply blood to the legs and feet narrow or become blocked and can cause pain, numbness, and tingling.
5. **Stroke:** Occurs when the blood supply to the brain is disrupted and can cause numbness, weakness and difficulty speaking.[10]
6. **Hypertension:** (high blood pressure) is when the pressure in your blood vessels is too high (140/90 mmHg or

higher). It is common but can be serious if not treated.[13]

- **STANDARD PHARMACOLOGICAL TREATMENTS**

As summarized above in this article, clopidogrel, warfarin, and statins (particularly simvastatin) and Betablockers are examples of how pharmacogenomics testing benefits patients with cardiovascular diseases.[8]

➢ **CLOPIDOGREL**

Clopidogrel is an inactive prodrug, which is activated in two oxidative steps by several cytochrome P450 (CYP) enzymes (such as CYP2C19, CYP1A2, CYP2B6, CYP2C9, and CYP3A). Clopidogrel irreversibly inhibits the P2Y12 subtype of adenosine diphosphate (ADP) receptor which is important in activation and aggregation of platelets and thus is used to reduce the risk of heart disease and stroke, and also following the placement of coronary artery stent.[11]

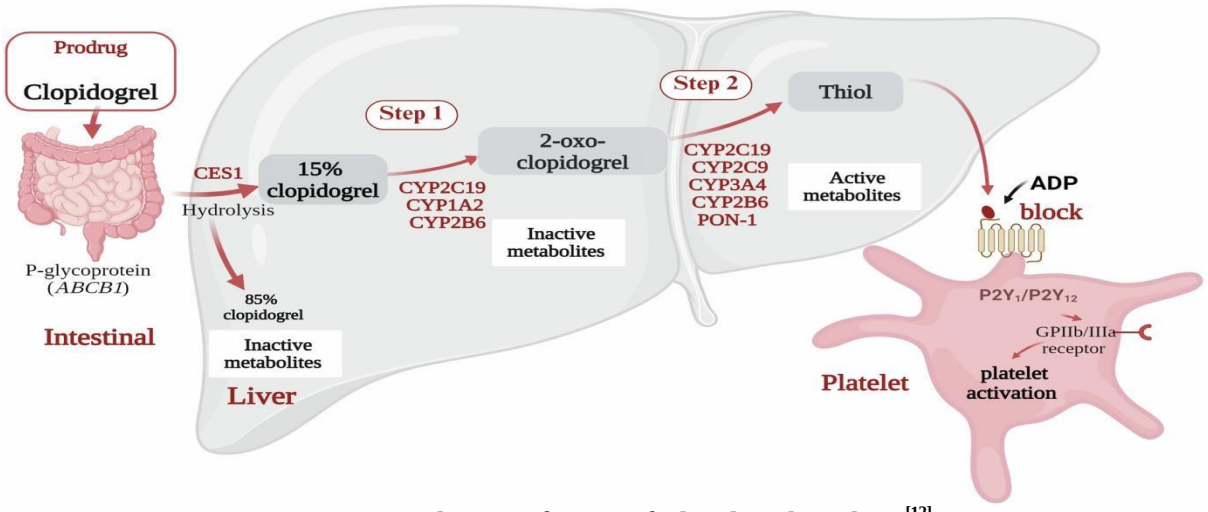

Figure 2: Mechanism of action of Clopidogrel Prodrug.[12]

➢ **WARFARIN**

Warfarin, the most used anticoagulant in patients with cardiovascular disease (CVDs), is prescribed for the treatment and prevention of thromboembolic events. The most common side effect of warfarin is bleeding. Variability in dose requirements for warfarin could be explained mainly by genetic variability.[11] Warfarin is given as a racemic mixture of its R and S isomers. The S isomer is three to five times stronger than the R isomer and is metabolised via a different pathway. CYP2C9 is the main enzyme involved in S-warfarin metabolic clearance, whereas CYP1A1, CYP1A2 and CYP3A4 are among the cytochrome P450 enzymes that remove R- warfarin.[12]

Many genes may influence warfarin metabolisms, among those, VKORC1, CYP2C9, and CYP4F2 are considered the main genes that cause genetic variations.[11]

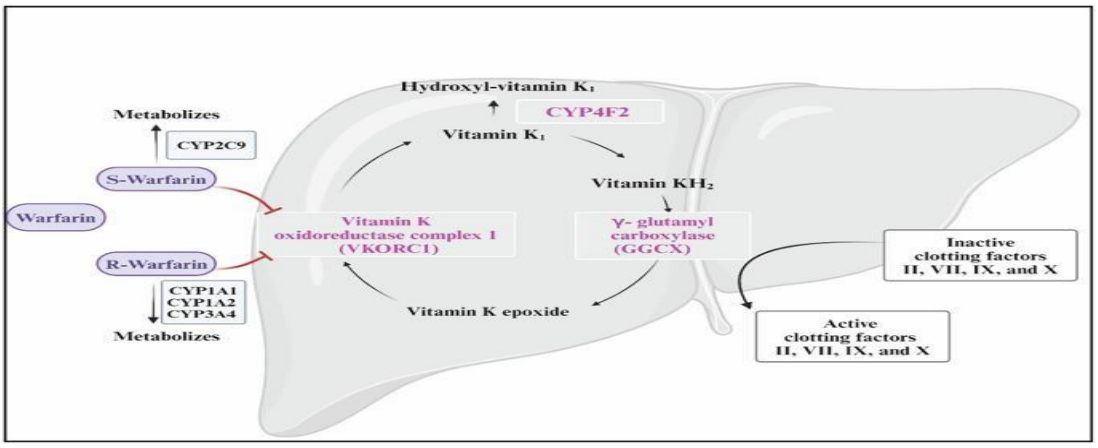

Figure 3: Mechanism of action of Warfarin.[12]

STATINS

Statins, also called 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are the first-line therapy for lowering lipid levels and reducing CVD risk. Statins exert their therapeutic effects by inhibiting the active site of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis, resulting in lower levels of low-density lipoprotein cholesterol (LDL-C) in the blood. The conversion of HMG-CoA to mevalonic acid is inhibited by preventing substrate access to this site, which leads to reduced hepatic cholesterol synthesis and upregulation of LDL receptors (LDLRs). This further leads to a decrease in the amount of LDL-C in the blood and an increase in LDL-C removal from circulation. However, not every patient responds well to statins, and some do not achieve their target cholesterol reduction levels. Moreover, a large proportion of patients experience side effects. Statin-induced myopathy (SIM) and statin-associated muscle symptoms (SAMs) are the most frequently reported side effects of statins, and these side effects result in poor adherence to or cessation of statin pharmacotherapy regimens.[12] There is significant interindividual variability in response to statins mainly due to single nucleotide polymorphisms (SNPs).[11]

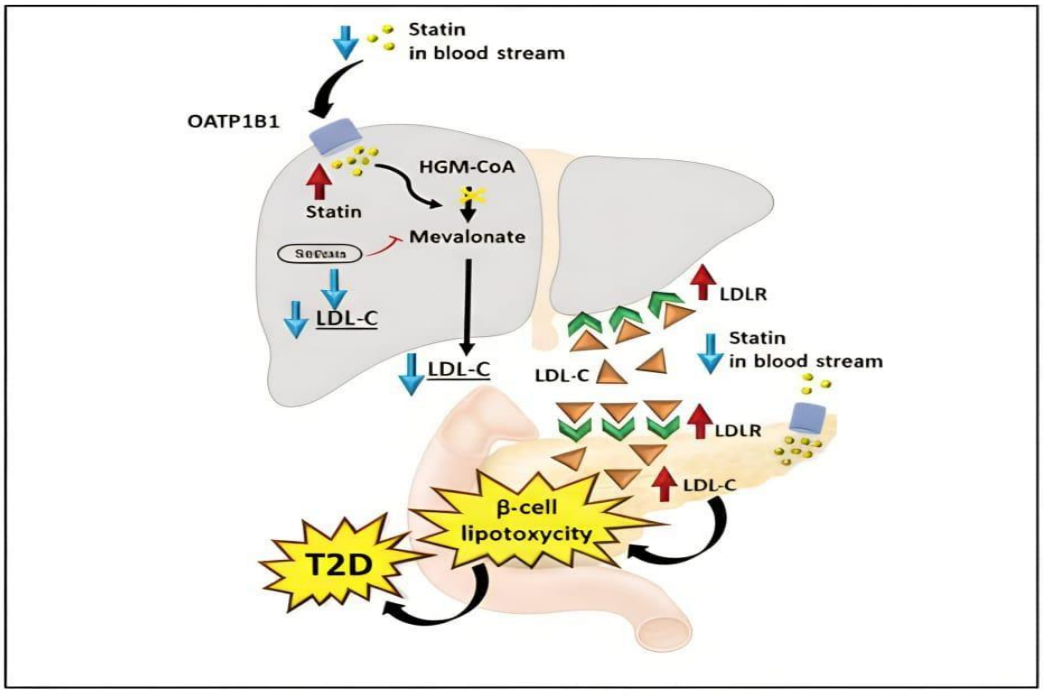

Figure 4: Mechanism of action of Statins.[14]

BETA BLOCKERS

Numerous investigations have verified a strong correlation between the HR-lowering effect of β-blockers and advantageous cardiovascular consequences. β-adrenergic receptors play a significant role in cardiac function via signal transduction controlled by G protein- coupled receptor kinase (GPCRK) phosphorylation interactions. The therapeutic goal of β- blockers is to prevent the binding of a ligand (catecholamines, either norepinephrine or epinephrine) to β-adrenergic receptors (β1AR and β2AR) by competing for the binding site. After the agonist binds to the βAR, it is linked to the Gs protein (Gαs) to activate adenyl cyclase (AC) and produce cyclic AMP (cAMP), which further phosphorylates GRK2 and then activates PKA, which in turn phosphorylates various intracellular substrates for practical function.The heart is the primary target of β-adrenergic receptor stimulation. When this receptor is activated, the contractility (inotropy), HR, and conduction velocity (homotopy) of the heart increase. The cardiovascular system can be better regulated by taking advantage of β1AR and β2AR signalling. When catecholamines overstimulate the β-adrenergic receptors, they cause CVD, stroke, heart failure, and cardiac enlargement. Elevating the level of Gα causes βAR kinase (βARK) to become active, which in turn influences and accelerates the development of heart failure by stimulating the cardiomyocyte βARs.[12]

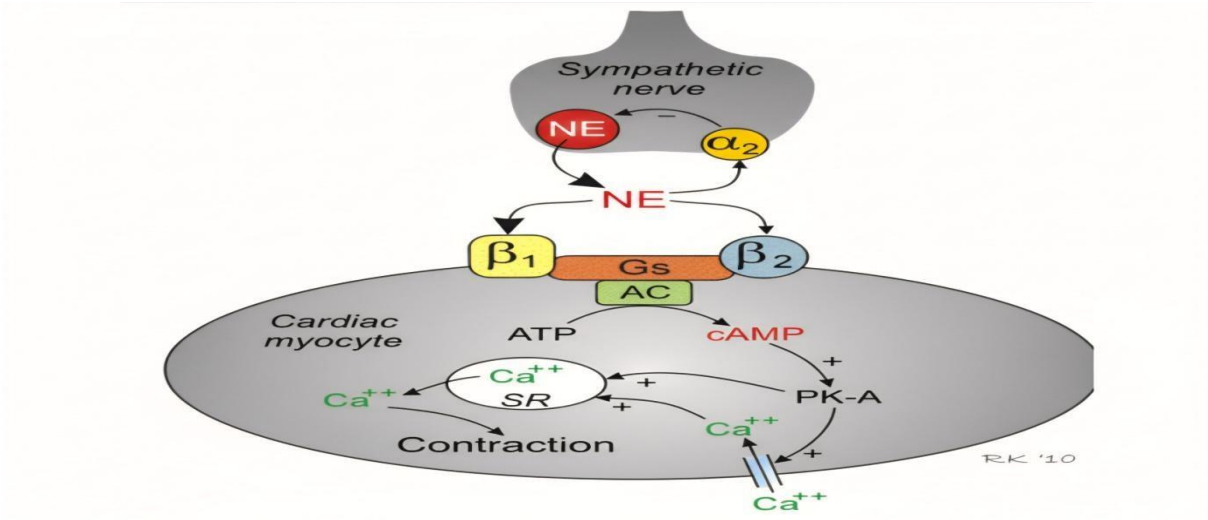

Figure 5: Mechanism of action of Beta Blockers.[15]

GENETIC VARIABILITY AND DRUG RESPONSE IN CVS THERAPY

Moreover, genetic variation can also affect drug target interactions, leading to variability in drug efficacy and therapeutic responses. Single nucleotide polymorphisms (SNPs) and structural variants in genes encoding drug targets (e.g., receptors, enzymes) can alter protein structure, function and drug binding affinity, influencing the pharmacological effects of drugs.[15]

Genetic polymorphisms affecting Clopidogrel response

Despite being one of the most widely used antiplatelet medications, clopidogrel has variable effects in certain patient populations. Genetic polymorphisms in CYP2C19 are among the main variables that influence an individual's response to clopidogrel.[12] Several genetic polymorphisms have been reported that may affect clopidogrel pharmacokinetics; including ABCB1 ,CES1 , CYP2C19 ,and paraoxonase-1(PON1). In addition, several P2Y12 gene mutations (such as H2 haplotype) have been identified to affect clopidogrel resistance. The CYP2C19 enzyme, encoded by the CYP2C19 gene, metabolizes Clopidogrel predominantly. CYP2C19*2 (G681A) and CYP2C19*3 (G636A) mutations

are the most common CYP2C19 loss-of-function alleles and CYP2C19*17 is the most common allele that results in increased enzyme activity. Therefore, based on the CYP2C19 genotypes, patients are categorized as ultrarapid metabolizer (*1/*17, *17/*17), extensive metabolizer (*1/*1), intermediate metabolizer (*1/*2, *1/*3, *2/*17), and poor metabolizer (*2/*2, *2/*3,*3/*3).Patients with CYP2C19 extensive metabolizer and ultrarapid metabolizer phenotypes are recommended to be treated with the standard dose of clopidogrel ,while those with a poor metabolizer phenotype will benefit from using an alternative antiplatelet agents(e.g., prasugrel or ticagrelor).[11]

A precision medicine strategy that used CYP2C19 genetic test results to deliver ticagrelor or prasugrel to LOF carriers and clopidogrel to non-carriers provided a more well-rounded therapeutic approach, as it lowered the risk of bleeding and ischaemic events compared to the universal use of ticagrelor or prasugrel.[12] Therefore, it has been suggested that using an alternative antiplatelet agent may improve cardiovascular outcomes in such patients.[11]

Genetic polymorphisms affecting Warfarin response

Genetic polymorphisms significantly influence dose requirements, yet they are infrequently incorporated into clinical practice. Warfarin was the first medication to have established pharmacogenetic dosing guidelines.[12]

Polymorphisms in the gene encoding the cytochrome P-450 2C9 enzyme (CYP2C9) are known to contribute to variability in sensitivity to warfarin. CYP2C9 is the enzyme primarily responsible for the metabolic clearance of the *S*-enantiomer of warfarin. Patients with certain common genetic variants of CYP2C9 require a lower dose of warfarin and a longer time to reach a stable dose. They are also at higher risk for over-anticoagulation and serious bleeding.[16]

Common polymorphisms in the gene Vitamin K epoxide Reductase Complex subunit 1 (VKORC1) affect warfarin dose response and blood clotting through effects on the formation of the reduced form of vitamin K, which subsequently alters carboxylation of vitamin K- dependent hemostatic and nonhemostatic proteins. Polymorphism in the VKORC1 gene explains 30% of the dosevariation between patients. A promoter polymorphism of VKORC1-1639G>A is present in linkage disequilibrium with VKORC1 1173C>T. This polymorphism in the promoter region alters the binding site for VKORC1 transcription factor and leads to lower VKORC1 mRNA expression and protein in human liver. As a result, the steady-state concentration of tissue VKOR decreases making a person with this variation more susceptible to inhibition by warfarin.

Individuals with CYP2C9 *1/*1, VKORC1 - 1639GG genotype are known to require the highest amount of weekly dose and are sometimes known as extensive or ultra-metabolizers. There is strong evidence that patients who are homozygous or heterozygous for CYP2C9*2, *3 or/and VKORC1 G - 1639A are sensitive to warfarin and acenocoumarol. They require low maintenance dose (CYP2C9*2, *3 carriers requiring reduction in dose by 16% and 41%for heterozygous and homozygous carriers, respectively) and take a longer time to achieve stable dose with international normalized ratio INR) values within the therapeutic range.[17]

Table 1: Detailed Guidance on Warfarin dosing based on CYP2C9 and VKORC1 genotypes.[17]

	CYP2C9

	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
VKORC1						
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
GA	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

Genetic polymorphisms affecting Statins response

CYP2C9 is responsible for the metabolism of certain statins, such as fluvastatin, pitavastatin, and rosuvastatin. Genetic variations in CYP2C9 affect the ability of an individual to metabolise these drugs. The two most extensively studied variants, CYP2C9*2 and CYP2C9*3, significantly metabolise statins more slowly, leading to higher drug levels and an increased risk of side effects. CYP2C9 genetic variations have been shown to impact statin exposure and the risk of SAMS. An SNP located in intron 13 of the HMG-CoA reductase gene causes an alternate splicing event that involves exon 13 within the catalytic domain of the enzyme to inhibit its activity.[12]

Simvastatin, atorvastatin, and lovastatin are primarily metabolized by cytochrome P450 (CYP) 3A enzymes. Significant associations between CYP3A polymorphisms and statin blood concentrations have been reported, and the US Food and Drug Administration-approved product and prescribing label for simvastatin clearly warns clinicians about the marked increase in the risk of simvastatin myotoxicity associated with concomitant use of CYP3A-inhibiting medications. In addition, other enzymes (CYPs and non-CYPs) are involved in the metabolism of certain statins.

Although less studied than CYP3A, those enzymes too can be significantly altered by the use of certain concomitant medications, resulting potentially in increased risk of statin adverse effects.[18]

Table 2: Recommended dosing of Simvastatin based on SLCO1B1 Phenotype.[18]

Phenotype	Genotype	Myopathy risk	Dosing recommendations
Normal Function , Homozygous wild type	TT	Normal	Prescribe desired starting dose and adjust dosage of simvastatin based on disease specific guidelines
Intermediate function, heterozygotes	TC	Intermediate	Prescribe a lower dose or consider an alternative statin (eg, pravastatin or rosuvastatin); consider routine CK surveillance
Low function, homozygous variant or mutant	CC	High	Prescribe a lower dose or consider an alternative statin (eg, pravastatin or rosuvastatin); consider routine CK surveillance.

Genetic polymorphisms affecting Beta blockers response

Several β-blockers, including metoprolol, carvedilol, propranolol, labetalol, nebivolol, and timolol, are substrates of the CYP2D6 enzyme. Metoprolol is a primary β-blocker whose pharmacokinetic variability, largely due to its dependence on CYP2D6 for metabolism, may lead to significant differences in pharmacodynamic responses among individuals. Many studies have shown that CYP2D6 poor and intermediate metabolizers exhibit decreased apparent oral clearance of metoprolol.

These pharmacokinetic differences primarily result in variations in heart rate (HR) response; however, other CYP2D6 phenotypes do not appear to significantly affect the response to β- blockers. The CYP2D6 genotype is linked to a changed HR response to β-blocker therapy, and it has been demonstrated that the CYP2D6 phenotype is one of the most important indicators of variation in HR response to metoprolol.

Notably, the HR indicates the level of β1AR blockade when β-blocker therapy is administered. The correlations between HR and CYP2D6 genotype were consistent, but the correlations between blood pressure and other responses were

weaker. However, some studies have shown a positive correlation between the CYP2D6 genotype and blood pressure response. Fewer studies are available related to individual variants of ADRA2C, GPCRK4, and GPCRK5 and their associations with β-blocker responses. Therefore, there is insufficient evidence to provide therapeutic recommendations for the individual variants of CYP2D6, ADRB2, ADRA2C, GPCRK4 and GPCRK5.[12]

The equivocal cause-effect relation between genetic polymorphisms in CYP2D6 and β-blocker response is reflected in the FDA label warning. For example, the label of Lopressor (metoprolol tartrate) states that the CYP2D6 dependent metabolism seems to have little or no effect on safety or tolerability of the drug. Nevertheless, heart failure patients that carry the loss-of- function CYP2D6 allele may be particularly vulnerable to high drug concentration and thus need to avoid β-blockers. Given the evidence of pharmacogenomic interactions between β- blockers and ADBR1 polymorphisms, combining multiple risk alleles may be more informative in managing β-blockers therapy.[8]

PHARMACOGENOMIC MARKERS IN CVD DRUGS

Table 3: Cardiovascular Pharmacogenomic targets with strong level of evidence.[3]

Gene	Variant	Drug	Drug response associated with risk allele
CYP2C19	(rs4244285)	Clopidogrel	Reduced active metabolite concentration Impaired platelet inhibition.
VKORC1−1639G>A	(rs9923231)	Warfarin	
CYP2C9*2	(rs1799853)	Warfarin	Reduced clearance of the potent S-Warfarin
CYP2C9*3	(rs1057910)	Warfarin	Reduced clearance of the potent S-Warfarin
SLC01B1	Rs4149056	Simvastatin	Impaired transporter function leading to increased simvastatin levels

CLINICAL APPLICATIONS AND GUIDELINES

The polygenic nature of drug response means that multiple genes and environmental factors often interact to determine an individual's response to a medication. As such, single-gene testing may not provide a complete picture.[19] This approach can replace the current practice of estimating dosage solely on weight and age parameters. Thus, pharmacogenetic techniques ensure that the patient receives the maximum therapeutic benefit from a particular drug while minimizing any unfavorable reactions or adverse effects. Dosage can thus be tailored to specific patient groups based on their available genetic information.[6] Effective PGx guided prescribing requires evidence from multiple sources to be distilled into guidelines and made available through clinical decision support systems(CDSS) that distil information on drug– gene interactions from published guidelines or prescribing labels. Clinical Pharmacogenetics Implementation Consortium(CPIC) and the Dutch Pharmacogenetics Working Groups(DPWG) have published guidelines covering 66 medications across several drug classes. However, the major PGx guideline and recommendation sources are not completely concordant in terms of their advice. A recent study found inconsistencies in clinical PGx recommendations (48.1%) and in 93.3% of recommendations from CPIC, FDA and clinical practice guidelines. These inconsistencies were spread across a range of domains- recommendation category(29.8%), the patient group(35.4%) and routine screening(15.2%), suggesting a potential barrier to rapid PGx implementation until this is resolved. CDSS is an effective tool to guide clinicians with limited PGx knowledge.[20]

Table 4: Drug-gene interactions and PGx guidelines.[21]

Drugs	Genes	PGx Guidelines
Clopidogrel	CYP2C19	CPIC, DPWG

Warfarin	CYP2C9, VKORC1	CPIC, CPNDS
Simvastatin	SLCO1B1	CPIC

CASE STUDIES

- **Clopidogrel and the CYP2C19 gene**

Clopidogrel is an antiplatelet prodrug used to prevent heart attacks and strokes in patients with CVD. It requires activation by the liver enzyme CYP2C19.[22]

Case study example

- A 58-year-old male with an ST-elevation myocardial infarction received clopidogrel after a Percutaneous Coronary Intervention (PCI).
- The patient experienced recurrent chest pain and repeat angiography revealed stent thrombosis, indicating clopidogrel failure.
- While his genotype in this specific case did not explain the failure, the overall evidence from similar cases led the U.S. Food and Drug Administration (FDA) to add a boxed warning to the clopidogrel label.

Personalized approach: Genotyping can identify poor metabolizers, for whom alternative antiplatelet agents, such as prasugrel or ticagrelor, are recommended.[23]

- **Warfarin and the CYP2C9 and VKORC1 genes**

Warfarin is an anticoagulant used to prevent thromboembolic events in conditions like atrial fibrillation. It has a narrow therapeutic index and requires careful dosing and monitoring.[24]

Case study example

- A 73-year-old Korean woman with atrial fibrillation experienced excessive anticoagulation and a high international normalized ratio (INR) at a standard warfarin dose.
- Genetic testing revealed a compound heterozygote genotype for \(CYP2C9*3\) and \(CYP2C9*4\), which significantly impaired warfarin metabolism.

Personalized approach: The patient's dose was substantially reduced to achieve a stable INR. This case highlights how genotyping can explain unusual responses and guide dosing decisions to improve patient safety and outcome.[25]

Conventional and personalized treatments for cardiovascular diseases (CVD) differ in their approach to patient care:
A normalized approach follows standardized, "one-size-fits-all" guidelines, while a personalized approach tailors therapies to an individual's unique biological and genetic profile.[11] The traditional approach to cardiovascular therapy has significant limitations. Conventional methods typically involve prescribing standard medications based on population averages, with subsequent adjustments made through trial and error. This approach often results in suboptimal responses, unnecessary side effects, and delayed therapeutic benefits. Research indicates that only a part of patients respond adequately to medications prescribed following the current standardized treatment strategy, underscoring the need for more personalized approaches, By incorporating genetic information into clinical decision-making, healthcare providers can select medications more likely to be effective for individual patients while avoiding those associated with adverse reactions based on their genetic profile.[29]

CHALLENGES AND LIMITATIONS

Challenges to Pharmacogenomic research

Despite the potential of the conduction of pharmacogenomics research in enhancing the effectiveness development of treatment strategies for patients is encouraged, such research is a complicated and challenging task. Further challenges in basic research concern a variety of additional influential factors that need to be addressed more systematically which pharmacogenomics has to overcome. However, pharmacogenomics is facing several challenges including ethical problems in its way. In this regard, there is various research aiming at resolving ethical issues in two fields of research and development and service provision to suggest and create some solutions.[2]

Challenges to Personalized medicine

There are a number of challenges associated with personalized medicines, especially with respect to obtaining their approval for routine use from various regulatory agencies. In addition, there have many issues associated with the broad acceptance of personalized medicines on the part of different health care stakeholders, such as physicians, health care executives, insurance companies, and, ultimately, patients. Almost all of these challenges revolve around a need to prove that personalized medicine strategies simply outperform traditional medicine strategies, especially many personalized therapies and can be very expensive. We also consider strategies for proving that personalized medicine protocols and strategies can outperform traditional medicine protocols and strategies.[26]

Table 5: Challenges in Pharmacogenomics.[27]

Challenges	Potential approaches
Establishing that drug responses are heritable	Twin studies; family studies -Linkage between drug response and genomic loci in cell lines, or model organisms
Defining candidate genes	Pharmacokinetic, Pharmacodynamic Drug targets Biological milieu in which drugs act Disease genes and pathways Whole genome approaches

Limitations

- While the current literature on pharmacogenomics in cardiac therapy highlights the promise of personalized treatment, many studies are limited by small sample sizes, which reduce the statistical power to detect meaningful gene–drug interactions. This is particularly problematic in trials assessing genotype-guided therapies for complex cardiovascular conditions, where multifactorial influences, such as environmental and epigenetic factors, can confound results.
- The majority of pharmacogenomic studies have focused on individuals of European and American descent, thereby limiting the generalizability of bindings to other ethnic groups.
- Moreover, the lack of long-term outcome data, such as reduction in thromboembolic or bleeding events, further complicates the translation of pharmacogenomic insights into routine practice. To advance the field, future studies must prioritize larger, multi- ethnic cohorts, standardized endpoints, and longitude.[29]
- **Genotyping Costs:** Genotyping costs, especially whole genome sequencing, are normally high, therefore not really suitable for mass application.
- **Data Interpretation:** The understanding of genetic information and the application of such information into clinical practice requires advanced bioinformatics tools and skilled personnel.
- **Lack of Standardized Guidelines:** The lack of consensus that advocates for the guidelines and the protocol for pharmacogenomic testing and its interpretation limits its uptake in the practice.

- **Greater effectiveness:** Treatment rather than merely prescribing medication is the goal in pharmacogenomics that prevents the use of those medications that do not respond.
- **Better results for the patients:** Personalized drug therapies may very drastically change the course of many diseases, including but not limited to oncology, cardiology, and psychiatry.[28]

ETHICAL, SOCIAL AND LEGAL CONSIDERATIONS

Pharmacogenomics represents a significant advancement in personalized medicine, particularly in the treatment of cardiovascular diseases. This approach, which studies how genetic variation affects drug response, promises to enhance treatment efficacy, reduce adverse events and optimize therapeutic regimens for individual patients. Approximately 95 % of the population carries one or more actionable pharmacogenetic variants, with over 75 % of adults over 50 years old taking medications with known pharmacogenomic associations.As cardiovascular pharmacogenomics moves from research to clinical implementation, numerous ethical, legal and social challenges have emerged that warrant careful consideration. These challenges include concerns about genetic discrimination, privacy protections, equitable access to testing, and the responsible use of genetic information in clinical decision-making.[29]

i. Ethical Considerations

The following are the ethical dimensions of conducting pharmacogenomic studies, especially in vulnerable populations.

- **Privacy and Data Security:** Protecting genetic information is of the utmost importance. Therefore, appropriate Texas Instruments patient's data protection policies and other measures have to be adopted.
- **Informed Consent:** A reasonable expectation is that individuals will understand the benefits and risks associated with pharmacogenomic tests before undergoing the test themselves. Discrimination: Everyone faces the potential threat of genetic discrimination, and it is possible that some people may be subjected to discrimination on the basis of their genetic background. This calls for proper measures to curb this occurrence.

ii. Legal considerations

- **Genetic Privacy:** Another major issue is the protection of genetic information from being accessed or shared with third parties without the consent of the individual. There is no doubt that laws and policies should be established for the protection of such genetic information and its responsible usage.
- **Liability and Negligence:** New developments in the application of pharmacogenomics might result to the emergence of liability and negligence related legal aspects. For instance, it is possible that adverse drug reactions or effects that could be prevented by pharmacogenomic screening can place liability on a health care provider.
- **Intellectual Property:** There is large capital injected in research and commercialization of pharmacogenomic devices. When it comes to encouraging innovations and more so researches, the issues of intellectual property, patents and copy rights have to be dealt with strategically.

iii. Social considerations

- **Genetic Discrimination:** With genetic information becoming widespread, there are fears of genetic discrimination which can disadvantage an individual in employment, medical insurance and other aspects.
- **Social Inequality:** Pharmacogenomic tests have an associated cost which may affect the availability of

personalized medicine creating a divide and exacerbating social inequality which already exists.

- **Public Health:** Overall, pharmacogenomics is a tool that can be used to advances health of the population through active patient management and treatment.[28]

RESEARCH TRENDS AND FUTURE PROSPECTIVES

Research trends

Pharmacogenomic research in the field of cardiovascular disease has been substantial over the past decade, with numerous Randomised clinical trails (RCTs) contributing to our understanding. Key drug–gene pairs of significance from a pharmacogenomic standpoint include warfarin with *CYP2C9* and *VKORC1*, clopidogrel with *CYP2C19* and high-dose simvastatin with *SLCO1B1*. Conversely, β-blockers and *CYP2D6* are not associated with clinically significant benefits in relation to other cardiovascular drugs. The integration of cutting-edge techniques such as whole-genome sequencing and Next generation screening and PRS analyses is poised to yield additional genetic insights supporting risk assessments and the case for pre-emptive genotyping in cardiovascular disease.[30]

Whole genome sequencing (WGS) and whole exome sequencing (WES) represent comprehensive approaches to genetic profiling that capture a broader spectrum of genetic variation. These technologies enable the identification of both common and rare variants across the genome, potentially uncovering previously unknown pharmacogenetic markers. The decreasing cost and increasing accessibility of WGS and WES have facilitated their application in research settings, with growing potential for clinical implementation NGS has revolutionized pharmacogenomic testing by enabling rapid, high-throughput analysis of multiple genes simultaneously.

This technology allows for comprehensive screening of relevant pharmacogenes, providing a more complete genetic profile than traditional single-gene testing approaches. NGS platforms can identify rare variants and novel polymorphisms that may influence drug responses. Beyond single-gene analysis, recent technological advancements have enabled the development of polygenic risk scores that incorporate multiple genetic variants to predict drug responses more accurately.[29] There are many centres which are implementing some of these drug–gene pairs into clinical practice, and evidence for the utility of these gene–drug pairs has been shown in both RCTs and real-world settings.[30]

Future Prospective

i. The future of pharmacogenomics in cardiac therapy holds immense promise, driven by ongoing advancements in genomic technologies and expanding clinical applications.
ii. Emerging technologies, such as NGS devices and AI-driven polygenic risk scoring, will enable faster, more cost-effective genetic profiling, allowing clinicians to tailor treatments with unprecedented precision.
iii. Additionally, multi-omics approaches combining genomics, transcriptomics, and metabolomics will uncover deeper mechanistic insights into drug responses, facilitating the development of novel biomarkers for cardiovascular drugs like DOACs, antiplatelet agents, and statins.
iv. Further integration of pharmacogenomics into healthcare systems will be accelerated by advancements in clinical decision support systems and electronic health record interoperability, ensuring genetic data is seamlessly incorporated into treatment planning.
v. The success of rapid genotyping initiatives, demonstrates the feasibility of point-of- care testing in acute settings, paving the way for broader adoption in emergency cardiovascular care.

vi. Future research will also focus on pharmacoepigenetics, exploring how environmental factors and lifestyle modifications interact with genetic predispositions to influence drug responses. As regulatory agencies increasingly endorse pharmacogenomic-guided therapies, insurance coverage for genetic testing will expand, reducing barriers to implementation.

vii. Ultimately, the convergence of these innovations will establish pharmacogenomics as a cornerstone of precision cardiology, reducing adverse drug reactions, improving patient outcomes, and optimizing healthcare resource utilization on a global scale.[29]

CONCLUSION

- In conclusion, Pharmacogenomics is at the forefront of personalized medicine, offering a future where treatments are tailored to each individual's genetic profile. By reducing adverse drug reactions, improving drug efficacy, and personalizing treatment plans, pharmacogenomics holds the promise of transforming healthcare.[31]
- Finally yet importantly, while the pharmacogenomics consider the health care outcomes of the individual patients as very important and therefore the interventions are patient centered, this would also be beneficial to the health care system by reducing costs associated with providers and shortening the time taken for drug development.[28]
- With increasing availability and decreasing cost, there is now a trend towards overall genetic testing for most commonly used medications and this is summarized in a clinically usable report. This makes it more accessible for the physician, as well as the patient and pharmacist.[4]

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