IJBPAS, March, 2025, 14(3): 1574-1594

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

PHARMACOGENOMICS OF HIGH ALERT CARDIOVASCULAR DRUGS

RUBASHREE K.B.[1] AND SRINIVAS K.[2*]

[1]Pharm D Intern, JKK Nattaraja College of Pharmacy, Kumarapalayam

[2]Assistant Professor, JKK Nattaraja College of Pharmacy, Kumarapalayam

Orcid Id: [1]0000-0003-2276-9876, [2]0009-0007-0292-9162

***Corresponding Author: Dr. K. Srinivas: E Mail: srinivaskalai1105@gmail.com**

Received 14th Nov. 2023; Revised 15th Dec. 2023; Accepted 15th May 2024; Available online 1st March 2025

https://doi.org/10.31032/IJBPAS/2025/14.3.8805

ABSTRACT

Pharmacogenomics plays a crucial role in understanding the interindividual variation in drug response and identifying genetic factors that affect drug reactions. In the context of cardiovascular drugs, which are commonly used to treat cardiovascular diseases, pharmacogenomics has the potential to optimize drug efficacy and minimize the risk of adverse reactions. Personalized medicine, which integrates genetic and genomic data with clinical and environmental factors, enables the identification of patients at risk for ADRs and the development of individualized treatment approaches. Pharmacogenomic studies have demonstrated positive results for many cardiovascular drugs, indicating that proactive testing can enhance efficacy and reduce toxicity risks. However, translating genetic test findings into treatment recommendations remains a challenge. High-alert cardiovascular drugs have a narrow therapeutic index and pose a high risk of harm if misused. This review focuses on the pharmacogenomics of high-alert cardiovascular drugs, including statins, antiplatelets, adrenergic antagonists, and antiarrhythmics. Understanding the pharmacogenomic factors influencing drug response can aid in tailoring treatment regimens to optimize patient outcomes and minimize adverse reactions in cardiovascular disease management.

Keywords: Pharmacogenomics, cardiovascular disease, high alert, drugs, treatment

INTRODUCTION

Cardiovascular disease necessitates a solid foundation in pharmacology, including pharmacokinetics, pharmacodynamics, and pharmacogenomics. Pharmacogenomics is the study of interindividual variation in drug reaction as a result of underlying genetic architecture. Genetic variations that affect human physiology or drug response may be targets for future drug research.

Age-related adverse drug reactions (ADRs) or therapeutic failure are becoming more common in older individuals. Due to the increased likelihood of drug-drug and drug-gene interactions, there may be a significant polypharmacy that mediates this. Precision medicine, which is based on individual genetic variations, allows the screening of patients at risk for ADRs and the implementation of personalised treatment regimens **[1, 2]**.

Personalised medicine combines genetic and genomic data with environmental and clinical variables to customize disease prevention and management strategies, including pharmacotherapy. Individualized treatment is made possible by the discovery of genetic variables that affect drug distribution, metabolism, excretion, and action at the drug target level. The majority of cardiovascular drugs (CVD) have reported positive pharmacogenomic results, indicating that proactive testing can increase efficacy and reduce the risk of toxicity. Changing the findings of genetic testing into treatment recommendations is the main challenge in pharmacogenomics **[3-5]**.

Cardiovascular drugs are used to treat a variety of diseases, but drug response and dosage requirements vary greatly between individual patients. A course of treatment that has been shown to be successful for one individual may be harmful or ineffective for another **[6]**.

High-alert medications are those that pose the greatest risk of causing harm if abused. The difference between a therapeutic dosage and a harmful dose for these medications is relatively small, or they have narrow therapeutic indices or small margins of safety **[7, 8]**.

In order to prevent, identify, and treat diseases, as well as to predict therapeutic response, nonresponse, and the probability of adverse reactions, personalised medicine uses data about a person's genes, proteins, and environment.

In the UK, cardiovascular disease is the main cause of mortality. For both primary and secondary disease prevention, numerous pharmacological therapies are given to an enormous number of patients. Therefore, the emphasis of this review describes progress in understanding genomic variability in response to high alert cardiovascular drugs and how this knowledge may be applied in clinical care.

This review will summarize recent advances in the pharmacogenomics of high alert cardiovascular drugs, with a focus on statins, antiplatelets, adrenergic antagonist and antiarrhythmics drugs.

Adrenergic antagonist

A class of drugs called adrenergic antagonists, commonly referred to as sympatholytic medicines, is used to block the actions of the sympathetic nervous system. These medications are frequently used to treat a number of conditions, such as anxiety, heart failure, and hypertension. However, a person's genetic make-up can have a significant impact on both their efficacy and safety. Pharmacogenomics research has been done to identify the genetic differences that affect the toxicity, effectiveness, and drug metabolism of adrenergic antagonists.

Beta blockers

Medications in the beta-blocker class are frequently prescribed to treat heart failure and hypertension. Some of the genetic variations were linked to improve blood pressure, while others were linked to a higher risk of unfavourable events like fatigue and shortness of breath. The pharmacokinetics and pharmacodynamics of beta-blockers are affected by differences in the genes involved in their metabolism and transport, such as CYP2D6 and ABCB1 **[9-12]**.

The pharmacokinetics and pharmacodynamics of beta-blockers have been showed to be influenced by genetic differences in the CYP2D6 gene, which encodes an enzyme involved in their metabolism. While ultra rapid metabolizers of CYP2D6 may need higher doses of beta-blockers to achieve therapeutic efficacy and poor metabolizers of CYP2D6 have a higher risk of adverse events like hypotension and bradycardia. The effectiveness of beta-blockers in the treatment of heart failure has also been linked to variations in the ABCB1 gene, which encodes a protein involved in the transport of medicines across the blood-brain barrier **[8-13]**.

Genetic variations in genes involved in signalling pathways and heart function have also been found as possible pharmacogenomic targets for beta-blockers, in addition to genetic variations in drug metabolism and transport genes. Patients taking beta-blockers for heart failure have a higher risk of adverse outcomes because of genetic differences in the G-protein-coupled receptor kinase 5 gene, which controls beta-1 adrenergic receptor desensitization. It has also been demonstrated that polymorphisms in the adrenergic receptor beta-2 gene influence how the body responds to beta-blockers which is used to treat hypertension. Metoprolol, carvedilol, timolol, and propranolol are a few examples of beta-

blockers that are metabolised by the CYP450 enzyme system. The CYP2D6 isoenzyme gene's polymorphisms may have an impact on blocker response. The effectiveness of beta-blockers as a treatment may be impacted by variations in the gene that codes for the 1-adrenergic receptor **[14-17]**.

ADBR2 encodes the beta-2-adrenergic receptor. R16G (rs1042713) and Q27G (rs1042714), two frequent ADBR2 polymorphisms, are resistant to agonist-mediated downregulation. Common ADRB2 polymorphisms have been linked to altered clinical cardiovascular outcomes, although these associations have not been verified. Some commonly prescribed beta-blockers, such as propranolol, timolol, and metoprolol, as well as the antiarrhythmic propafenone, which has beta-blocking properties, are metabolised by CYP2D6. Numerous loss-of-function mutations exist in the gene, and people who have two of these mutationsroughly 7% of Caucasians and Africansare referred to as poor metabolizers. When compared to noncarriers (Q41Q), the L41Q variant of GRK5 blunts the effects of catecholamines and is linked to better outcomes in heart failure **[18-20]**.

Ser49Gly and Arg389Gly are two single nucleotide polymorphisms (SNPs) that result in altered biological function in vitro, including increased agonist-induced adenylyl cyclase activation by Gly49 compared to Ser49 and by Arg389 compared to Gly389. The beta-1 adrenergic receptor (ADRB1) gene has the functionally significant polymorphisms. Prior to the Ser49Gly polymorphism (rs1801252), which is located on the extracellular region of the receptor, the common polymorphism Arg389Gly (rs1801253) is connected with a higher activity of the receptor and greater desensitisation and downregulation with long-term stimulation. The ADRB1 gene's Arg389Gly polymorphism impacts how well patients respond to betablocker medication. In a few studies, it was discovered that 389 Arg carriers, as opposed to Gly 389 carriers, significantly improved their left ventricular ejection fraction in response to beta-blockers in healthy volunteers, hypertensive patients, and patients with systolic heart failure **[21-29]**.

The beta-2 adrenergic receptor (ADRB2) has two functionally significant polymorphisms: Arg16Gly (rs104213) and Gln27Glu (rs1042714). Thr164Ile (rs1800888), a third polymorphism in ADRB2, was also discovered. The two frequent polymorphisms in the ARDB2 gene, Arg16Gly (rs104213) and Gln27Glu (rs1042714), did not appear to be associated with improvements in left ventricular ejection fraction in response to beta-blockers in the majority of investigations. Only a few small studies compared the

Gln27 allele to the Glu27 allele in terms of the left ventricular ejection fraction following beta-blocker treatment **[30-31]**.

Propronolol

Cytochrome P450 (CYP) enzymes, particularly CYP2D6 and CYP1A2, are principally responsible for the metabolism of propranolol. Propranolol can be metabolised differently due to genetic differences in these enzymes, altering drug exposure and possibly altering medication efficacy. There is, however, no evidence that any enzyme can improve propranolol activity. Propranolol's antagonistic effects on beta-adrenergic receptors, which lower blood pressure and heart rate, are the primary causes of its pharmacological effects.

People who have genetic variations in CYP2D6 may have a higher risk of toxicity than people who normally metabolise propranolol well. Similar to other CYP1A2 inhibitors, fluvoxamine and ciprofloxacin can raise propranolol levels in the blood and cause toxicity. Propranolol is one example of a parent drug that is metabolised by cytochrome P-450 isoenzyme 2D6; the CYP2D6*4 polymorphism results in decreased activity of a metabolising enzyme and may increase plasma concentrations of the parent drug and decrease amounts of metabolites. Toxic development could result from this in the future.

Labetolol

Labetalol is a medicine that is used to treat hypertension and angina. It has alpha-1 blocking activity and is a non-selective beta blocker. Large-scale first-pass metabolism of labetalol occurs in the liver, where it is largely glucuronidated and, to a lesser extent, oxidised by cytochrome P450 (CYP) enzymes. Rather than enzyme activity, labetalol's activity is mostly influenced by its pharmacokinetic and pharmacodynamic characteristics.

It is possible for labetalol to interact with other drugs that are metabolised by CYP enzymes, such as calcium channel blockers and amiodarone, increasing labetalol exposure and raising the risk of toxicities.

Alpha-blockers

Alpha-blockers are drugs that inhibit the effects of alpha-adrenergic receptors, which are responsible for the sympathetic nervous system's vasoconstriction. Alpha-blockers are frequently used to treat benign prostatic hyperplasia and hypertension. However, a person's genetic make-up can have a significant impact on both their efficacy and safety.

Compared to beta-blockers, alpha-blockers' pharmacogenomics is less well understood, however a number of genetic variants that affect medication metabolism, effectiveness, and toxicity have been found. The alpha-1 adrenergic receptor gene, which encodes the alpha-1 adrenergic receptor, is an important pharmacogenomic target for alpha-blockers.

Certain genetic variations were linked to improved blood pressure control, whereas others were linked to a higher risk of unfavourable events like orthostatic hypotension and vertigo. The pharmacokinetics and pharmacodynamics of alpha-blockers are affected by differences in the genes involved in their metabolism and transport, such as CYP3A4 and ABCB1. Alpha-blockers are metabolised by an enzyme that is encoded by the CYP3A4 gene. Genetic variants in this gene have been demonstrated to affect the pharmacokinetics and pharmacodynamics of these medications. Alpha-blocker dosages may need to be increased in ultrarapid CYP3A4 metabolizers in order to attain therapeutic efficacy, whereas poor metabolizers may be more likely to have side effects such hypotension and vertigo. Alpha-blocker effectiveness in the treatment of hypertension has also been linked to variations in the ABCB1 gene, which encodes a protein involved in drug transport across the blood-brain barrier.

Genes involved in signalling pathways and vascular function have also been identified as possible pharmacogenomic targets for alpha-blockers, in addition to genetic variations in drug metabolism and transport genes. Patients taking alpha-blockers for hypertension have an increased risk of adverse outcomes due to genetic differences in the nitric oxide synthase 3 gene. It has also been demonstrated that variations in the endothelin-1 gene alter when alpha-blockers react in curing Raynaud's phenomenon **[14-17]**.

Antiplatelets

In patients undergoing dual anti-platelet medication, the GP Ia C807T polymorphism is linked to the expression of this collagen receptor on the platelet membrane surface, and both polymorphisms are linked to higher platelet reactivity. The ADP subtype P2Y1 receptor (C893T) polymorphism is linked to decreased platelet aggregation after aspirin ingestion, however there isn't any clinical evidence to support this. According to the literature, platelet function may be impacted by hemostatic variables. In comparison to Leu34-negative individuals, Leu34 carriers (Val34Leu polymorphism of factor XIII) receiving low-dose aspirin therapy have a lower risk of developing an acute myocardial infarction **[32-33]**.

Aspirin

According to a study, aspirin responses are compromised in PLA2 (Leu59Pro) carriers, a variation of platelet glycoprotein IIIa. After seven days of aspirin therapy in healthy volunteers, 23 of 25 PLA1 homozygotes had lower plasma prothrombin fragment concentrations in bleeding-time wounds than 9 of 15 PLA2 carriers. Aspirin responses are compromised in 8 PLA2 (Leu59Pro) carriers, a variation of platelet glycoprotein IIIa **[32-35]**.

Clopidogrel

The most frequently prescribed antiplatelet medication is clopidogrel. A thienopyridine derivative called clopidogrel specifically inhibits ADP-dependent platelet activation and aggregation by binding irreversibly to the platelet P2RY12 purinergic receptor. The genes implicated in clopidogrel metabolism are the apparent candidates for pharmacogenetic study **[36]**.

As a prodrug, clopidogrel is converted into its active form, thiol, in the liver during the process of biotransformation. In this process, CYP1A2, CYP2C19, CYP3A4/5, and CYP2B6 are all active. P2Y12 belongs to the adenosine diphosphate (ADP) G protein-coupled purinergic receptor. The P2Y12 protein, a crucial regulator of blood clotting, is mostly, though not entirely, present on the surface of blood platelets. Platelet ADP P2Y12 receptors are irreversibly bound by the active clopidogrel metabolite. Increased enzyme transcription and improved clopidogrel responsiveness are both related to the YP2C19*17 allele. The risk of bleeding is higher among carriers of this allele, who may be protected from MACE.

Clopidogrel biochemical reaction was found to be mostly determined by ADP P2Y12 receptors and CYP2C19*2 loss-of-function, which accounted for 12% of the variation in ADP-stimulated platelet aggregation during treatment. Clopidogrel treatment increases the incidence of significant adverse cardiovascular events and stent thrombosis in CYP2C19*2 carriers compared to noncarriers. Clopidogrel patients with loss-of-function CYP2C19*2 allele have decreased conversion of the drug into its active metabolite, diminished antiplatelet efficacy, and increased risk for cardiovascular events **[37-41]**.

In Caucasians, African Americans, and Mexicans, the prevalence of the CYP2C19*2 polymorphism ranges from 18% to 33% (2%–3% homozygotes), while the allele frequency is higher in Asians. The loss-of-function *3 variation, which is more common among Asians, is similarly linked to a worse response.The ABCB1 gene in humans is responsible for encoding the glycoprotein 8 P, also known as the multidrug resistance protein 1 (MDR1), ATP-binding cassette subfamily B member 1, or cluster of differentiation 243 (CD243) **[42-45]**.

The CYP2C19 functional SNP genotype identifies patient subgroups at increased risk of ischemic events following percutaneous intervention (PCI) when taking clopidogrel. The xenobiotic efflux p-glycoprotein pump implicated in clopidogrel intestinal absorption is encoded by the ABCB1 gene (also known as MDR1). The reaction to clopidogrel has been inconsistently linked to the C3435T polymorphism. Lower peak plasma concentrations of clopidogrel and its

active metabolites have been linked to the 3435TT genotype **[46-48]**.

Paraoxonase-1, an esterase produced in the liver and connected to HDL in the blood, is encoded for by the PON1 gene. A group of researchers revealed findings from in vitro metabolomic profiling that suggested paraoxonase-1 was crucial for the bioactivation of clopidogrel from the intermediate product created by the liver's cytochromes to the active metabolite in the bloodstream. The rate-limiting enzyme that transforms 2-oxo-clopidogrel into the active metabolite is called paraoxonase 1 (encoded by PON1). Lower paraoxonase 1 activity, lower levels of the active clopidogrel metabolite, and reduced platelet inhibition are all observed in 192Gln allele carriers **[49-54]**.

The PON1 Q192R polymorphism was later linked to an increased risk of ischemia events in clopidogrel-treated individuals in clinical investigations carried out by the same team. The hypothesis that paraoxonase-1 participates in the bioactivation of clopidogrel has since been challenged by further pharmacology research. Additionally, later clinical studies did not provide evidence that the Q192R polymorphism affected cardiovascular outcomes in patients taking clopidogrel **[49-54]**.

According to Bouman *et al*., patients with the Gln192Gln polymorphism had a hazard ratio of 12.9 for risk of stent thrombosis compared to patients with an Arg192Arg polymorphism. This polymorphism was reported to be connected with clopidogrel-associated stent thrombosis. This outcome was not supported by additional research. The PON1- Gln192Arg polymorphism has been shown to have no significant effect on the risk of MACE and does not modify the physiologic response to clopidogrel in patients receiving clopidogrel treatment **[55]**.

Statins

Hydroxymethylglutaryl-coenzyme when administered for both primary and secondary prevention of ischemic heart disease, a reductase inhibitors (statins) have been shown to decrease coronary and cerebrovascular events as well as overall mortality. The effectiveness of the medication is correlated with a number of well-known gene polymorphisms. A gene that codes for cholesteryl ester transfer protein (CETP), which is involved in the metabolism of high-density lipoprotein (HDL), was the subject of some research that looked at polymorphism **[56-57]**.

Patients taking pravastatin who had either the B1/B1 or B1/B2 genotype (B1 polymorphism present or absent) experienced significantly slower atherosclerotic progression than those taking a placebo. Patients with the B2/B2 genotype who received placebo experienced the slowest progression. However, patients

with the B2/B2 genotype who were taking pravastatin (16% of the study population) did not experience any benefits **[58-59]**.

Variants in the SLCO1B1 and CYP3A5 genes, which are involved in solute carrier organic anion transport, may be used to predict myotoxicity. Variations in statin efficacy have been linked to genetic variations in CYP3A4, which metabolises simvastatin, atorvastatin, and lovastatin. Lower LDL cholesterol levels with atorvastatin have been linked to the CYP3A4*4 haplotype as well as a nonsynonymous polymorphism (M445T). Statins do not appear to decrease cholesterol in people who have either the CYP3A4*1G haplotype or the CYP3A4 promoter polymorphism (A290G) **[60-61]**.

Medical professionals are concerned about statin-related myotoxicity, particularly rhabdomyolysis, because it necessitates changing drugs and stopping treatment. Variants in the CYP3A5 and solute carrier organic anion transporter family (SLCO1B1) genes have been identified to have the potential to predict myotoxicity. With beta-blockers versus calcium channel blockers, myocardial infarction or stroke was found to be associated with the calcium signalling genes CACNA1C, CACNB2, and KCNMB1. Patients on lisinopril had variable stroke risk by genotype for an MMP3 promoter polymorphism, while thiazides and beta-blockers had varying treatment-related outcomes but not diltiazem, depending on the NEDD4L (protein decrease renal tubular expression of epithelial Na+ channel) genotype **[63-68]**.

A decrease in the lowering of LDLc has been linked to variations in HMGCR and LDLR. Other gene variation has also been sporadically linked to variation in statin responsiveness. These include CYP3A4, which codes for a crucial drug metabolising enzyme, APOE, which codes for a protein that interacts with the LDL receptor, and ABCB1 and ABCG2, which code for drug transporters. The increased risk of coronary events, improved LDLc response to pravastatin, and a 30% reduction in the relative risk of cardiovascular events compared to noncarriers who were also treated with pravastatin have all been linked by numerous reports to a missense variant, Trp719Arg rs20455, in the kinesin-like protein 6 (encoded by KIF6) **[69-73]**.

Rare PCSK9 polymorphisms have been linked to low LDLc and a reduced risk of cardiovascular disease, and the protein is currently being targeted to create new cholesterol-lowering drugs **[74]**.

The organic anion transporting polypeptides B1 (OATP1B1), which are expressed on the sinusoidal membrane of hepatocytes and help the liver absorb numerous statins, are encoded by this gene. People who carry the CC genotype have a higher risk of developing myopathy than TT carriers do.

However, the presence of myopathy does not require the risk SLCO1B1 allele, suggesting that other variants of the same gene or other genes may also be important **[75-78]**.

A GWAS found a strong correlation between a noncoding polymorphism (rs4363657) and statin-induced myopathy in patients on high doses of simvastatin. Statin responsiveness is correlated with haplotypes. The c388A-c521T haplotype is referred to as the *1A (reference haplotype), the *1B (c388G-c521T), the *5 (c388Ac521C), and the *15 (c388G-c521C). Carriers of *5 have a 2- to 3-fold higher chance of developing creatine kinase-negative myopathy and a 4- to 5-fold higher risk of developing severe simvastatin-induced myopathy. Variability in the response to statin therapy has been linked to genetic variations in the CYP3A4 enzyme, which metabolises simvastatin, atorvastatin, and lovastatin **[79-80, 36]**.

Polymorphism of atorvastatin (M445T) and the CYP3A4*4 haplotype were linked to reduced levels of low density lipoprotein cholesterol. Statins do not appear to decrease cholesterol in people who have the CYP3A4*1G haplotype or the CYP3A4 promoter polymorphism (A290G). 2. 56 The efflux transporter multidrug resistance protein MDR1 (gene name ABCB1) or another efflux protein from the same family (gene name ABCG2) are substrates for several statins. Simvastatin's effectiveness in hypercholesterolemic patients is affected by ABCB1 variations, and patients who have negative muscular effects were less likely to have the ABCB1 polymorphisms (1236T, 2677 non-G, and 3435T). Atorvastatin and rosuvastatin's pharmacokinetics are affected by ABCG2 variations. Comparatively to those with AA genotypes, individuals with CC genotypes at rs2231142 (ABCG2 polymorphism) experienced larger reductions in LDL cholesterol levels **[81-83]**.

Kinesin-like protein 6 is a protein involved in the intracellular transport of many molecules, including mRNA. It is a member of the molecular motor superfamily. A few studies have found a link between coronary artery disease and the rs20455 polymorphism in the KIF6 (Trp719Arg) gene as well as a protective effect of statin administration in Trp719Arg carriers. Unfortunately, a meta-analysis of 19 studies failed to confirm the link between non-fatal coronary artery disease and the kinesin-like protein 6 (KIF6) Trp719Arg polymorphism (rs20455) **[84]**.

Antiarrhythmics

Numerous antiarrhythmic medications have adverse effects on the sodium and potassium ion channels in the heart. Genetic differences are linked to a risk of proarrhythmic effects of antiarrhythmic medicines and its mechanism. Drug-induced arrhythmia typically increases with

increasing drug concentrations, indicating the involvement of liver enzyme polymorphisms. Some evidence suggests that polymorphisms in genes encoding components of cardiac ion channels have been associated with congenital arrhythmia syndromes, such as long-QT and idiopathic ventricular fibrillation syndromes. The CYP2D6 gene controls the cytochrome P450 metabolic pathways, and some research suggests a link between the phenotype of a poor metabolizer and the toxicity of antiarrhythmic medications **[85]**. The sodium and potassium ion channels in the heart are negatively impacted by antiarrhythmic medications. Genetic differences are linked to a risk of proarrhythmic effects of antiarrhythmic medicines and its mechanism. Congenital arrhythmia has reportedly been linked to polymorphisms in genes encoding cardiac ion channel components **[86-89]**.

During treatment with dihydropyridine calcium channel blockers, a NOS1AP variant in the gene encoding an accessory protein for neuronal nitric oxide synthase was linked to total and cardiovascular mortality. The risk of arrhythmias in patients with the congenital long QT syndrome has also been observed to be modulated by variations in NOS1AP, at equivalent QT interval durations, as well as the risk of sudden death in the general population.

Congenital long QT syndrome (cLQTS)-related gene variation is overrepresented in acquired long QT syndrome cases. The potassium channel subunit gene KCNE1 D85N variant was reported to have an odds ratio of 9–12 for this ADR in a sizable candidate gene investigation. Another investigation linked alterations in the NOS1AP gene, which controls the baseline QT interval, to increased risk of amiodarone-induced TdP **[90-96]**.

CONCLUSION

The overall administration of high alert medications necessitates heightened care and particular precautions due to the very tight therapeutic margin of safety and potential serious patient damage. Using pharmacogenomic data to personalise medicine is a highly intriguing concept. The discovery of pharmacogenetics/ pharmacogenomics has increased our understanding of the molecular mechanisms driving the toxicity and effectiveness of widely prescribed CV medications. Personalised medicine based on pharmacogenomics has the potential to significantly improve the health and economic well-being of patients, particularly the elderly, medical professionals, and society as a whole. Its widespread application necessitates the knowledge and skill of physicians and scientists in genetics, risk prediction, and genetic counselling.

AUTHOR DECLAARATION

We declare that this review has been composed solely by ourself and that it has not been submitted, in whole or in part, in any previous application for a degree. Except where states otherwise by reference or acknowledgment, the work presented is entirely by us.

REFERENCES:

[1] Caudle KE, Dunnenberger HM, Freimuth RR, *et al*. standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). Genet Med. 2017; 19:215-23.

[2] Brockmöller J, Stingl JC. Multimorbidity, polypharmacy and pharmacogenomics in old age. Pharmacogenomics. 2017; 18:515-7.

[3] Roses, A D. Pharmacogenetics and the practice of medicine. Nature. 2000; 405(1):857-865.

[4] Evans WE, Johnson JA. Pharmacogenomics: the inherited basis for inter-individual variability in drug response. Ann Rev Genomics hum Genet. 2001; 2(1):9-39.

[5] Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. Science. 286(1):487-491.

[6] Real-Time PCR Research Solutions for Pharmacogenomics. Thermo fisher scientific. Published in 2023. Accessed on April 24, 2023. Available at https://www.thermofisher.com/in/en/home/clinical/clinical-translational-research/pharmacogenomics/real-time-pcr-solutions-pharmacogenomics.html?gclid=Cj0KCQjw ib2mBhDWARIsAPZUn_knUX1a MaTZNsnYmgEK-ymHju2QaGb0ncWojD2AbFeC-6NFiMpmGxoaAm2q EALw_wcB&cid=gsd_gts_sbu_r01 _co_cp1552_pjt10889_col025313_ 0se_gaw_rs_cdn_pgx&ef_id=Cj0K CQj wib2mBhDWARIsAPZUn_knUX1 aMaTZNsnYmgEK-ymHju2QaGb0ncWojD2AbFeC-6NFiMpmGxoaAm2 qEALw_wcB:G:s&s_kwcid=AL!36 52!3!663983336820!b!!g!!pharmac ogenomics!20316723033!15156258 6438.

[7] Rohani BI, Wan Mohaina Binti Wan Mohammmad, Mohd Azuwan Bin Mohd Zubir. Guideline on safe use of High Alert Medications. Available at www.pharmacy.gov 2011; 1-19.

[8] Salmon N. Medical Error Reduction A Key to Quality Care. Advanced care staffing. Published in 2022. Accessed on April 24, 2023. Available at https://advancedcarestaffing.com/wp-content/uploads/2018/04/Medical-Error-Reduction-Key-to-Quality-Care-by-RN.com_.pdf.

[9] Lennard MS, Silas JH, Freestone S, Ramsay LE, Tucker GT, Woods HF. Oxidation phenotype- a major determinant of metoprolol metabolism and response. N Engl J Med. 1982; 307:1558-1560.

[10] Lennard MS, Silas JH, Freestone S, Ramsay LE, Tucker GT, Woods HF. Differential stereoselective metabolism of metoprolol in extensive and poor debrisoquin metabolizers. Clin Pharmacol. Ther. 1983; 34:732-737.

[11] Silas JH, Lennard MS, Tucker GT, Ramsay LE, Woods HF. Polymorphic metabolism of beta adrenoceptor antagonists. Br J Clin Pharmacol. 1984; 17(1):11S-19S.

[12] Labbe L, O Hara G, Lefebvre M, *et al*. Pharmacokinetics and pharmacodynamic interaction between mexiletine and propafenone in human beings. Clin Pharmacol Ther. 2000; 68:44-47.

[13] Johnson JA, Burlew BS. Metoprolol metabolism via cytochrome P4502D6 in ethnic populations. Drug metab dispos. 1996; 24:350-355.

[14] Lanfear DE, Spertus JA, McLeod HL. Beta2-adrenergic receptor genotype pre- dicts survival: implications and future directions. J Cardiovasc Nurs. 2006; 21:474-477.

[15] Pacanowski MA, Gong Y, Cooper-Dehoff RM, *et al*. Beta-adrenergic receptor gene polymorphisms and be- ta-blocker treatment outcomes in hypertension. Clin Pharmacol Ther. 2008; 84:715-721.

[16] Lemaitre RN, Heckbert SR, Sotoodehnia N, *et al*. Beta1- and beta2-adrenergic receptor gene variation, beta-blocker use and risk of myocardial in- farction and stroke. Am J Hypertens. 2008; 21:290-296.

[17] Lemaitre RN, Siscovick DS, Psaty BM, *et al*. Inhaled beta-2 adrenergic receptor ago- nists and primary cardiac arrest. Am J Med. 2002; 113:711-716.

[18] Green SA, Turki J, Innis M, *et al*. Amino-terminal polymorphisms of the human beta 2-adrenergic receptor impart distinct agonist-

promoted regulatory properties. Biochemistry. 1994; 33:9414–19.

[19] de Groote P, Helbecque N, Lamblin N, *et al*. Association between beta-1 and beta-2 adrenergic receptor gene polymorphisms and the response to beta-blockade in patients with stable congestive heart failure. Pharmacogenet. Genomics.2005; 15:137–42.

[20] Small KM, Wagoner LE, Levin AM, *et al*. Synergistic polymorphisms of beta1- and alpha2Cadrenergic receptors and the risk of congestive heart failure. N. Engl. J. Med. 2002; 347:1135–42.

[21] Maqbool A, Hall AS, Ball SG, Balmforth AJ. Common polymorphisms of beta1-adrenoceptor: identification and rapid screening assay. Lancet. 1999;353(9156):897.

[22] Drysdale CM, McGraw DW, Stack CB, *et al*. Complex promoter and coding region beta 2-adrenergic receptor haplotypes alter receptor expression and predict in vivo responsiveness. Proc Natl Acad Sci U S A. 2000;97(19):10483-10488.

[23] Mason DA, Moore JD, Green SA, Liggett SB. A gain-of-function polymorphism in a G-protein coupling domain of the human beta1-adrenergic receptor. J Biol Chem. 1999;274(18):12670-12674.

[24] Bengtsson K, Melander O, Orho-Melander M, *et al*. Polymorphism in the beta(1)-adrenergic receptor gene and hypertension. Circulation. 2001;104(2):187-190.

[25] Humma LM, Puckett BJ, Richardson HE, *et al*. Effects of beta1-adrenoceptor genetic polymorphisms on resting hemodynamics in patients undergoing diagnostic testing for ischemia. Am J Cardiol. 2001;88(9):1034-1037.

[26] Li GH, Faulhaber HD, Rosenthal M, *et al*. Beta-2 adrenergic receptor gene variations and blood pressure under stress in normal twins. Psychophysiology. 2001;38(3):485-489.

[27] L Busjahn A, Li GH, Faulhaber HD, *et al*. beta-2 adrenergic receptor gene variations, blood pressure, and heart size in normal twins. Hypertension. 2000;35(2):555-560.

[28] Timmermann B, Mo R, Luft FC, *et al*. Beta-2 adrenoceptor genetic variation is associated with genetic predisposition to essential hypertension: The Bergen Blood

Pressure Study. Kidney Int. 1998;53(6):1455-1460.

[29] Plato CF. Alpha-2 and beta-adrenergic receptors mediate NE's biphasic effects on rat thick ascending limb chloride flux. Am J Physiol Regul Integr Comp Physiol. 2001;281(3):R979-R986.

[30] Brodde OE. Beta-1 and beta-2 adrenoceptor polymorphisms: functional impor- tance, impact on cardiovascular diseases and drug responses. Pharmacol Ther. 2008; 117:1-29.

[31] Liu J, Liu ZQ, Tan ZR, *et al*. Gly389Arg polymorphism of beta1-adrenergic receptor is associated with the cardiovascular re- sponse to metoprolol. Clin Pharmacol Ther. 2003; 74:372-379.

[32] Undas A, Sanak M, Musial J, Szczeklik A. Platelet glycoprotein IIIa polymor- phism, aspirin, and thrombin generation. Lancet. 1999; 353:982-983.

[33] Goodman T, Ferro A, Sharma P. Pharmacogenetics of aspirin resistance: a com- prehensive systematic review. Br J Clin Pharmacol. 2008; 66:222-232.

[34] Goodall AH, Curzen N, Panesar M, *et al*. Increased binding of fibrinogen to glycoprotein IIIa-proline33 (HPA-1b, PlA2, Zwb) positive platelets in patients with cardiovascular disease. Eur Heart J. 1999; 20:742-747.

[35] Walter DH, Schachinger V, Elsner M, Dimmeler S, Zeiher AM. Platelet glyco- protein IIIa polymorphisms and risk of coronary stent thrombosis. Lancet. 1997; 350:1217-1219.

[36] Scott SA, Sangkuhl K, Gardner EE, *et al*. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. Clin. Pharmacol. Ther. 2011; 90:328–32.

[37] Farid NA, Kurihara A, Wrighton SA. Metabolism and disposition of the thienopyridine antiplatelet drugs ticlopidine, clopidogrel, and prasugrel in humans. J Clin Pharmacol. 2010; 50(2): 126–42.

[38] Mega JL, Close SL, Wiviott SD, *et al*. Cytochrome P450 polymorphisms and response to clopidogrel. N Engl J Med. 2009; 360: 354–62.

[39] Simon T, Verstuyft C, Mary-Krause M, *et al*. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med. 2009; 360: 363–75.

[40] Collet JP, Hulot JS, Pena A, *et al*. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet. 2009; 373: 309–17.

[41] Sibbing D, Stegherr J, Latz W, *et al*. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. Eur Heart J. 2009; 30: 916–22.

[42] Santos PC, Soares RA, Santos DB, *et al*. CYP2C19 and ABCB1 gene polymorphisms are differ- ently distributed according to ethnicity in the Brazilian general population. BMC Med Genet. 2011; 12:13.

[43] Kubica A, Kozinski M, Grzesk G, Fabiszak T, Navarese EP, Goch A. Genetic determinants of platelet response to clopidogrel. J Thromb Thrombolysis. 2011; 32:459-466.

[44] Pare G, Mehta SR, Yusuf S, *et al*. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. N Engl J Med. 2010; 363(18):1704- 1714.

[45] Bhatt DL, Pare G, Eikelboom JW, *et al*. The relationship between CYP2C19 polymorphisms and ischaemic and bleeding outcomes in stable outpatients: the CHARISMA genetics study. Eur Heart J. 2012; 33(17):2143-2150.

[46] Taubert D, von Beckerath N, Grimberg G, *et al*. Impact of P-glycoprotein on clopidogrel absorption. Clin Pharmacol Ther. 2006; 80(5):486-501.

[47] Mega JL, Close SL, Wiviott SD, *et al*. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. Lancet. 2010;376(9749):1312-1319.

[48] Wallentin L, James S, Storey RF, *et al*. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet (London, England). 2010 Oct;376(9749):1320-1328.

[49] Snoep JD, Hovens MMC, Eikenboom JCJ, van der Bom JG, Jukema JW, Huisman MV. Clopidogrel nonresponsiveness in patients undergoing percutaneous coronary intervention with stenting: a systematic review and metaanalysis. Am Heart J. 2007; 154(2): 221–31.

[50] Bouman HJ, Schömig E, van Werkum JW, *et al*. Paraoxonase-1 is a major determinant of clopidogrel efficacy. Nat Med. 2011; 17: 110–16.

[51] Lewis JP, Fisch AS, Ryan K, *et al*. Paraoxonase 1 (PON1) gene variants are not associated with clopidogrel response. Clin Pharmacol Ther. 2011; 90: 568–74.

[52] Trenk D, Hochholzer W, Fromm MF, *et al*. Paraoxonase-1 Q192R polymorphism and antiplatelet effects of clopidogrel in patients undergoing elective coronary stent placement. Circ Cardiovasc Genet. 2011; 4: 429–36.

[53] Simon T, Steg PG, Becquemont L, Verstuyft *et al*. Effect of paraoxonase-1 polymorphism on clinical outcomes in patients treated with clopidogrel after an acute myocardial infarction. Clin Pharmacol Ther. 2011; 90: 561–7.

[54] Reny JL, Combescure C, Daali Y, Fontana P. PON1 Meta-Analysis Group. Influence of the paraoxonase-1 Q192R genetic variant on clopidogrel responsiveness and recurrent cardiovascular events: a systematic review and meta-analysis. J Thromb Haemost. 2012; 10(7): 1242–51.

[55] Bouman HJ, Schomig E, van Werkum JW, *et al*. Paraoxonase-1 is a major determinant of clopidogrel efficacy. Nat Med. 2011;17(1):110- 116.

[56] Verschuren JJ, Trompet S, Wessels JA, *et al*. A systematic review on pharmacogenetics in cardiovascular disease: is it ready for clinical application? Eur Heart J. 2011; 33: 165–75.

[57] Voora D, Ginsburg GS. Clinical application of cardiovascular pharmacogenetics. J Am Coll Cardiol. 2012; 60(1): 9–20.

[58] Boekholdt SM, Kuivenhoven JA, Hovingh GK, Jukema JW, Kastelein JJ, van Tol A. CETP gene variation: relation to lipid parameters and cardiovascular risk. Curr Opin Lipidol. 2004; 15:393-398.

[59] Kuivenhoven JA, Hovingh GK, van Tol A, *et al*. Heterozygosity for ABCA1 gene mutations: effects on enzymes, apoli- poproteins and lipoprotein particle size. Atherosclerosis. 2003; 171:311-319.

[60] Rebbeck TR, Jaffe JM, Walker AH, Wein AJ, Malkowicz SB. Modification of clinical presentation of prostate tumors by a novel genetic variant in CYP3A4

[published correction appears in J Natl Cancer Inst 1999 Jun 16;91(12):1082]. J Natl Cancer Inst. 1998;90(16):1225-1229.

[61] Roden DM, Wilke RA, Kroemer HK, Stein CM. Pharmacogenomics: the genetics of variable drug responses. Circulation. 2011;123(15):1661-1670.

[62] Wilke RA, Moore JH, Burmester JK. Relative impact of CYP3A genotype and concomitant medication on the severity of atorvastatin-induced muscle damage. Pharmacogenet Genomics. 2005; 15:415-421.

[63] Pasanen MK, Neuvonen M, Neuvonen PJ, Niemi M. SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. Pharmacogenet Genomics. 2006; 16:873-879.

[64] Voora D, Shah SH, Spasojevic I, *et al*. The SLCO1B1*5 genetic variant is associated with statin-induced side effects. J Am Coll Cardiol. 2009; 54:1609-1616.

[65] Donnelly LA, Doney AS, Tavendale R, *et al*. Common nonsynonymous sub- stitutions in SLCO1B1 predispose to statin intolerance in routinely treated individuals with type 2 diabetes: a go-DARTS study. Clin Pharmacol Ther. 2011; 89:210-216.

[66] Beitelshees AL, Gong Y, Wang D, *et al*. KCNMB1 genotype influen- ces response to verapamil SR and adverse outcomes in the INternational VErapamil SR/Trandolapril STudy (INVEST). Pharmacogenet Genomics. 2007; 17:719-729.

[67] Beitelshees AL, Navare H, Wang D, *et al*. CACNA1C gene polymorphisms, cardiovascular disease outcomes, and treatment response. Circ Car- diovasc Genet. 2009; 2:362-370.

[68] Niu Y, Gong Y, Langaee TY, *et al*. Genetic variation in the beta2 subunit of the voltage-gated calcium channel and pharmacogenetic association with adverse cardi- ovascular outcomes in the INternational VErapamil SR-Trandolapril STudy GENEtic Substudy (INVEST-GENES). Circ Cardiovasc Genet. 2010; 3:548-555.

[69] Poduri A, Khullar M, Bahl A, Sehrawat BS, Sharma Y, Talwar. Common variants of HMGCR, CETP, APOAI, ABCB1, CYP3A4, and CYP7A1 genes as predic- tors of lipid-lowering response to

atorvastatin therapy. DNA Cell Biol. 2010; 29:629-637.

[70] Gerdes LU, Gerdes C, Kervinen K, *et al*. The apolipoprotein epsilon4 allele determines prognosis and the effect on prognosis of simvastatin in survivors of myocardial infarction : a substudy of the Scandinavian simvastatin survival study. Circulation. 2000.; 101:1366-1371.

[71] Donnelly LA, Doney AS, Dannfald J, *et al*. A paucimorphic variant in the HMG-CoA reductase gene is associ- ated with lipid-lowering response to statin treatment in diabetes: a GoDARTS study. Pharmacogenet Genomics. 2008; 18:1021-1026.

[72] Krauss RM, Mangravite LM, Smith JD, *et al*. Variation in the 3-hydroxyl-3-methylglutaryl coenzyme a reduc- tase gene is associated with racial differences in low-density lipoprotein cholesterol response to simvastatin treatment. Circulation. 2008; 117:1537-1544.

[73] Mangravite LM, Wilke RA, Zhang J, Krauss RM. Pharmacogenomics of statin response. Curr Opin Mol Ther. 2008; 10:555-561.

[74] Cohen JC, Hobbs HH. Simple genetics for a complex disease. Science. 2013; 340:689–90.

[75] Ramsey LB, Johnson SG, Caudle KE, *et al*. The clinical pharmacogenetics implementation consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. Clin Pharmacol Ther. 2014; 96:423-8.

[76] Voora D, Shah SH, Spasojevic I, al. The SLCO1B1*5 genetic variant is associated with statin-induced side effects. J Am Coll Cardiol. 2009; 54:1609-16.

[77] Wilke RA, Ramsey LB, Johnson SG, *et al*. Clinical Pharmacogenomics Implementation Consortium (CPIC). The clinical pharmacogenomics implementation consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. Clin Pharmacol Ther. 2012; 92:112-7.

[78] Mirosevic SN, Macolic SV, Simic I, Ganoci L, Muacevic Katanec D, Bozina N. ABCG2 gene polymorphisms as risk factors for atorvastatin adverse reactions: a case-control study.

Pharmacogenomics. 2015; 16:803-15.

[79] Sibbing D, Koch W, Gebhard D, *et al*. Cytochrome 2C19∗17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. Circulation. 2010; 121:512–18.

[80] Wallentin L, James S, Storey RF, *et al*. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet. 2010; 376:1320–28.

[81] Kajinami K, Brousseau ME, Ordovas JM, Schaefer EJ. CYP3A4 genotypes and plasma lipoprotein levels before and after treatment with atorvastatin in primary hy- percholesterolemia. Am J Cardiol. 2004; 93:104-107.

[82] Wang A, Yu BN, Luo CH, *et al*. Ile118Val genetic polymorphism of CYP3A4 and its effects on lipid-lower- ing efficacy of simvastatin in Chinese hyperlipidemic patients. Eur J Clin Pharmacol. 2005; 60:843-848.

[83] Gao Y, Zhang LR, Fu Q. CYP3A4*1G polymorphism is associated with lipidlowering efficacy of atorvastatin but not of simvastatin. Eur J Clin Pharmacol. 2008; 64:877-882.

[84]] Li Y, Sabatine MS, Tong CH, *et al*. Genetic variants in the KIF6 region and coronary event reduction from statin therapy. Hum Genet. 2011; 129:17-23.

[85] Priori SG, Barhanin J, Hauer RN, *et al*. Ge- netic and molecular basis of cardiac arrhythmias: impact on clinical management parts I and II. Circulation. 1999; 99:518-528.

[86] Napolitano C, Schwartz PJ, Brown AM, *et al*. Evidence for a cardiac ion channel mutation underlying drug-induced QT prolongation and life-threatening arrhythmias. J Cardiovasc Electrophysiol. 2000;11(6):691-696.

[87] Drici MD, Barhanin J. Cardiac K+ channels and drug-acquired long QT syndrome. Therapie. 2000;55(1):185-193.

[88] Abbott GW, Sesti F, Splawski I, *et al*. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. Cell. 1999;97(2):175-187.

[89] Escande D. Pharmacogenetics of cardiac K(+) channels. Eur J Pharmacol. 2000;410(2-3):281-

287. doi:10.1016/s0014-2999(00)00821-9.

[90] Roden DM. Long QT syndrome: reduced repolarization reserve and the genet- ic link. J Intern Med. 2006; 259:59-69.

[91] Paulussen AD, Gilissen RA, Armstrong M, *et al*. Genetic variations of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in drug-induced long QT syndrome patients. J Mol Med (Berl). 2004; 82:182-188.

[92] Yang P, Kanki H, Drolet B, *et al*. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. Circulation. 2002; 105:1943-1948.

[93] Itoh H, Sakaguchi T, Ding WG, *et al*. Latent genetic backgrounds and molecular pathogenesis in drug-induced long-QT syn- drome. Circ Arrhythm Electrophysiol. 2009; 2:511-523.

[94] Becker ML, Visser LE, Newton-Cheh C, *et al*. A common NOS1AP genetic polymorphism is associated with in- creased cardiovascular mortality in users of dihydropyridine calcium channel block- ers. Br J Clin Pharmacol. 2009; 67:61-67.

[95] Crotti L, Monti MC, Insolia R, *et al*. NOS1AP is a genetic modifier of the long-QT syn- drome. Circulation. 2009; 120:1657-1663.

[96] Tomas M, Napolitano C, De Giuli L, *et al*. Polymorphisms in the NOS1AP gene modulate QT interval duration and risk of arrhythmias in the long QT syndrome. J Am Coll Cardiol. 2010; 55:2745-2752.