Chapter 3

Drug Interactions, Pharmacogenomics and Cardiovascular Complication

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Additional information is available at the end of the chapter

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1. Introduction

Early identification of patients who will be at a higher risk for the development of adverse side effects and who will need dosage adjustment has the potential to help the clinician to limit a patient's exposure to drug side effects. When on multiple medications and complex regimens, cardiac patients are at increased risk and particularly vulnerable to drug interactions. A rational and informed approach to drug interactions, based on scientific knowledge, can reduce the chance of adverse effects and improve patient outcomes.

Cardiovascular drugs are used to treat various forms of illnesses, but there are often large differences between individual patients in drug response and dosage requirement. Treatment that has been proven effective for one person can be ineffective or even dangerous for another.

A drug produces its therapeutic effect when it reaches its target concentration in the bloodstream. Whether a steady therapeutic concentration is obtained largely depends on the balance between the dose administered and the rate at which the body metabolises the drug. An individual patient's response to a drug is not totally predictable. Below the target therapeutic range, a drug may be ineffective or, when it is higher, the drug may cause adverse reactions or become toxic. To ensure the safe and effective action of many drugs, the concentration in the bloodstream and their clinical effects are monitored. If necessary, the dose can be adjusted or the medication changed to achieve the best possible outcome.

To avoid unintended and untoward adverse drug reactions, the prescriber should use the fundamental principles of pharmacology and pharmacogenetics. Several drugs are metabolised through the same pathways and knowledge of the potential pathway capacity could help to predict treatment success. Variability in the reaction to medication may be due to

age, gender, morbidity, co-medication, food components, smoking and environmental factors. However, polymorphisms present in genes, are responsible for most of the variation. Pharmacogenetic research and candidate gene approaches have succeeded in the identification of several genetic factors influencing treatment response. In particular, associations between variants in CYP enzymes and transporter genes have been repeatedly associated with different response and treatment--associated side effects [1-6]. Knowledge of pharmacogenomics is providing a key to understanding fundamentals of the drug interaction process.

A specific genotype might differ in its frequency in different ethnic populations, leading to differences in drug response. However, gene combination between ethnic groups makes it impossible for the practitioner to simply predict if a drug will be efficient or not. There is no specific genetic definition of ethnicity and ethnicity does not sufficiently separate those for whom a given therapy will be effective.

In contrast, the pharmacogenetics potentially presents a more effective way of identifying responders, nonresponders and potential adverse drug reactions. Pharmacogenetics provides defined clinical biomakers for individualised therapy [7].

Personalised medicine can be defined as a form of medicine that uses information about a person's genes, proteins and environment to prevent, diagnose and treat diseases, including predicting therapeutic response, nonresponse and likelihood of adverse reactions. Diagnostic biomarkers are necessary to successfully select patients for therapy, distinguish likely responders from nonresponders, identify patients at high risk for adverse events, or select an appropriate dose for safe and efficacious use of the therapy.

The human genome consists of approximately 3 billion base pairs (NCBI database) and the sequence of these varies among individuals. These variations can change the function of proteins that interact with a drug and hence, the response to a drug may differ among individuals. Sequence variations in drug-disposition genes can alter the pharmacokinetics of a drug and those in drug-target genes can change the pharmacodynamics of a drug.

When a genetic polymorphism alters the function of a protein that is involved in the absorption, metabolism, distribution and excretion of a drug, the concentrations of the parent drug or its active metabolites may be affected. For example, *CYP2D6**4 polymorphism leads to lower activity of a metabolising enzyme and the plasma concentrations of the parent drug metabolised by cytochrome P-450 isoenzyme 2D6 may increase and concentration of metabolites may decrease (some antidepressants). As a result, it could lead to the development of toxicity. For prodrugs, when metabolites have pharmacologic activity, the genetic polymorphism may reduce the drug response (some analgesics). Genetic polymorphisms that change the activity of the drug target (pharmacodynamics) may also alter the drug response. For example, vitamin K epoxide reductase complex subunit 1 gene polymorphisms influence warfarin response and β_1-adrenergic receptor gene polymorphisms after β-blocker response. Therefore, drugs can compete for binding sites on the receptors or be metabolised by the same enzyme, consequently create dug-drug interaction problem.

The information about pharmacogenetic terms and recourses is presented in the Appendix.

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Early identification of patients who will be at a higher risk for the development of adverse side effects and who will need dosage adjustment has the potential to help the clinician to limit a patient's exposure to drug side effects. Characterisation of drug metabolising polymorphisms has been shown to be useful for identifying individuals who are poor drug metabolisers and at risk of developing adverse reactions, and several genotyping methods are already being used in clinical settings (Table1). The evidence provided by pharmacogenetics and pharmacogenomics can be successfully used for drug interaction interpretation.

Drugs	**Tests of polymorphisms**	**Affected WSLHD Population***
Wafarin	CYP2C9	1% - Poor Metabolisers, 15% - Intermediate
Phenytoin		
Warfarin	VKORC1	11% with altered function
Clopidogrel	*CYP2C19*	4% - Poor Metabolisers, 13% - Intermediate, 20% - Ultra fast metabolisers
Carvedilol	CYP2D6	5% - Poor Metabolisers, 27% - Intermidiate, 1% - Ultra fast metabolisers
Metoprolol		
Propafenone		
Propranolol		
Quinidine		
Isosorbide	NAT1, NAT2	10-90%
Hydralazine		
Warfarin	Protein C Deficiencies	1/200 population, 2-5% Patients with Venous Thromboembolism
Atorvastatin	LDLR	1-5% Familial Cholesterolemia Patients
Statins	SINM PhyzioType (50 genes)	10-30% Patients on statin (multi-gene biomarker system manufacture results, no data available)

Table 1. Available Pharmacogenetics tests for cardiovascular medication. (*Western Sydney Population combined data. WSLHD population is a mix of Caucasians, Asians and Africans.)

2. Hypertensive drugs

Hypertension is a common condition associated with increased risk of stroke, heart failure, ischemic heart disease, and chronic renal failure. Thiazide diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) are a common first line treatment for hypertension [8].

Despite availability of many effective agents, only about 40 percent [9] of treated hypertensive patients have their blood pressure controlled, mostly due to the unpredictable individual responses to treatment. Blood pressure responses to monotherapy vary widely within ethnic and gender subgroups [10].

Numerous studies have tried to establish associations between genetic polymorphisms and response to antihypertensive drugs. New developments in pharmacogenetics and pharmacogenomics already offer in pharmacogenetics and pharmacogenomics already offers the opportunity to provide individualised drug therapy on the basis of a person's genetic make-up for some drugs, despite varied approaches in study designs and methodology. These tests are provided by several laboratories and available at some hospitals; pharmacogenetic methods will not only help to achieve treatment goals and limit adverse effects, but also avoid drug interactions.

2.1. β-blockers

β-blockers through binding to β-adrenergic receptors (BAR) antagonise the binding of endogenous agonists. Variations in the gene encoding the β1-adrenergic receptor probably influence the treatment outcome. Two single nucleotide polymorphism (SNPs), resulting in Ser49Gly and Arg389Gly were identified and these variants demonstrate altered biological function in vitro, including enhanced agonist induced adenylyl cyclase activation by Gly49 compared to Ser49 and by Arg389 compared to Gly389 [11].

Some studies have shown that the Arg389Arg genotype and Ser49/Arg389 haplotype are associated with a greater response to blood pressure-lowering metoprolol [12].

The differential survival of Acute Coronary Syndrome (ACS) patients treated with β-blockers was associated with patients' β-adrenergic receptors 2 variant Gly16Arg and Gln27Glu genotypes; however, β-adrenergic receptors 1 variants showed no significant associations [13, 14].

No significant correlation has been found for outcomes of death, MI or stroke in coronary artery disease patients on atenolol treatment and β-adrenergic receptors variants or haplotypes [15] and β-adrenergic receptors 2 variants in MI and stroke outcomes. However, the case-control study found significant interaction with two SNPs in β-adrenergic receptors variant and cardiovascular complications [16, 17].

Angiotensin-converting enzyme (ACE) genes variations were also associated with β-blockers therapy outcome. In heart failure, patients survival without a transplant, has been associated with the angiotensin-converting enzyme I/D genotype (insertion/deletion).

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Patients with the D allele may derive greater benefits from pharmacologic interventions with Beta-blocker treatment, probably through the decrease of sympathetic nervous system activity [18].

The effects of the CYP450 enzyme systems has been studied intensively during the last years and its role in the metabolism of drugs and other endogenous and exogenous chemicals is well defined. Numerous publications confirm the association of these enzymes with drug-drug, drug-toxins and drug-food interactions. Polymorphisms in the gene coding for the CYP2D6 isoenzyme, which catalyses the metabolism of β-blockers such as metoprolol, carvedilol, timolol, and propranolol, may also affect blocker response. It has been demonstrated that the clearance of the R(+) enantiomer of carvedilol was 66% lower and the area under the concentration-versus-time curve 156% higher among poor metabolizers than extensive metabolizers [19-22].

Some studies showed association with other genes. Genes involved in calcium signalling - CACNA1C, CACNB2, and KCNMB1- were found to be associated with myocardial infarction or stroke with β-blockers versus calcium channel blockers [23-25]. Variable stroke risk by genotype was described for an MMP3 promoter polymorphism in patients treated with lisinopril [26] and different treatment-related outcomes with thiazides and β-blockers, but not diltiazem, by NEDD4L (protein reduce renal tubular expression of epithelial Na+ channel) genotype [27].

Finally, the two studies by Schelleman et al reported no β-blocker interactions (for outcomes MI or stroke) variants of angiotensin receptor II type 1 (AGTR1) and ACE [28, 29].

2.2. Diuretics

Diuretics may act at a number of sites, including the proximal tubule, the Loop of Henle, and the distal and collecting tubules. Diuretics are thought to indirectly activate the renin-angiotensin-aldosterone system and block sensitivity of blood vessels to catecholamines. Thiazide diuretics are the drug of choice for initial therapy, but genes responsible for renal sodium reabsorption can affect the patient's responsiveness to diuretic therapy.

Antihypertensive response in black African Americans is found to be associated with locus at chromosome12q15 [30, 31] where the FRS2 gene is located, which is involved in fibroblast growth factor signalling. FRS2 plays a role in vascular smooth muscle cell regulation.

Genome-wide association (GWA) studies are aimed at identifying common genetic variants modulating disease susceptibility, physiological traits and variable drug responses. These studies also provide further evidence for the large effects that single gene variants may exert for some drugs. GWA has explained relatively large proportions of variability compared to studies of traits such as disease susceptibility or physiological measurements. GWAS demonstrated that SNPs in lysozyme and Yeats domain-containing protein 4 (YEATS4) were associated with response to diuretic [30].

Lynch et al. found that C carriers of the NPPA T2238C variant, which codes for the precursor of atrial natriuretic polypeptide, had more favourable clinical outcomes when treated

with a diuretic, whereas individuals homozygous for the T allele responded better to a calcium channel blocker [32].

Patients with SNP of T594M gene (epithelial sodium channel) variant responded more favourably to amiloride therapy for BP control than to thiazide-based drugs. In cases of severe hypokalemia, potassium-sparing diuretics such as amiloride or triamterene should be used according to serum sodium and potassium levels [33, 34].

NEDD4L is also a candidate gene with a documented functional SNP, a role in sodium reabsorption, and several studies have found an association between this SNP and blood pressure response with thiazides [27, 35].

A common functional polymorphism resulting in Gly460Trp in the α-adducin gene ADD1 has been associated with response to thiazides. This finding led to the development of a novel antihypertensive drug class targeting adducin [36, 37]. Manunta et al. performed single SNP association analysis and combination analysis on ADD1 (Gly460Trp), NEDD4L, WNK1 in a 4-week diuretic trial. They found ADD1 460Trp carriers had significantly greater BP reduction than Gly460 homozygotes. When considered together, there was a significant trend in decreases of systolic blood pressure (SBP) (ranging from −3.4 mm Hg to −23.2 mm Hg) for different combinations of genotypes [35].The ADD1 Gly460Trp polymorphism has been associated with an increased risk of myocardial infarction or stroke during thiazide diuretic treatment [38] In contrast, these findings were not confirmed by other studies [39, 40].

The 825T allele in the G-protein is probably associated with a sodium-sensitive form of hypertension. Blood pressure declines for both the C/T and T/T genotypes were significantly greater than for the C/C genotype. The study revealed that the decreases in blood pressure varied on the basis of genotype and even after multiple regression analysis, genotype remained a significant predictor of blood pressure lowering [41].

2.3. Renin-angiotensin system inhibitors

Numerous genes from the renin-angiotensin system (RAS) pathway have been shown to play a key role in the regulation of blood pressure and influence the cardiovascular system. Several pharmacogenetic studies of the RAS were conducted. However, due to the complexity of RAS, associations between drug efficiency and polymorphisms are not consistent [42-45].

Angiotensin-converting enzyme (ACE) inhibitors prevent the conversion of angiotensin I to angiotensin II in plasma and tissue and prevent the degradation of bradykinin. Clinically, ACE inhibitors reduce peripheral vascular resistance and pulmonary capillary wedge pressure and increase cardiac output and renal blood flow. Treatment with ACE inhibitors in hypertension has been associated with improvements in vascular compliance, regression of left ventricular hypertrophy, improved systolic and diastolic function, and improvements in insulin sensitivity [46]. One study showed that ACE DD polymorphism is associated with poor collateral circulation (PCC). PCC in patients carrying the D allele may be associated with endothelial dysfunction and elevated blood ACE levels in these patients [47].

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The insertion/deletion (I/D) in the angiotensin I-converting enzyme (ACE) gene is one of the candidates for studies. The D allele has been associated with more improvement in coronary endothelial dysfunction with ACE inhibitor therapy than the I allele [48]. Reductions in systolic and diastolic blood pressures were significantly greater for patients with the D/D genotype than for patients with the I/D and I/I genotypes [49].

Diastolic blood pressure tended to decrease more for the ACE I/I genotype than for other ACE genotypes and the I/I genotype was also predictive of greater diastolic blood pressure decline [50]. Decline in renal function during ACE inhibitor treatment tended to be greater in heart failure patients with the ACE I/I genotype [51]. The I/I genotype has also been associated with increased susceptibility to the development of cough during ACE inhibitor therapy. After four weeks of therapy with an ACE inhibitor in healthy volunteers, the threshold for cough was significantly reduced for the I/I genotype but not the D/D genotype [52].

Another gene of interest is the angiotensinogen (AGT) gene. It was reported that the angiotensinogen 235Met/Thr polymorphism is also associated with RAS activity and drug responses. In subjects on ACE inhibitor monotherapy with 235Thr allele the response is higher than in the control group. Systolic and diastolic blood pressures were higher and the likelihood of using two or more antihypertensive medications was 2.1 times higher with the 235Thr polymorphism [53].

An association with polymorphisms in the angiotensin AT1 receptor (AGT1R) gene and ACE inhibitors' efficiency are found in some studies. The AGT1R mediates some negative effects of angiotensin II, such as vasoconstriction, cardiac remodelling, and aldosterone secretion. Angiotensin II blockers bind to angiotensin II receptors, thereby antagonizing the effect of angiotensin II, a potent vasoconstrictor [54]. The 1166C allele of AGT1R has been associated with increased arterial responsiveness to angiotensin II in ischemic heart disease and increased aortic stiffness in hypertension. During ACE inhibitor treatment, reductions in aortic stiffness were reported to be three times greater in carriers of the 1166C allele than in 1166A homozygotes [55, 56]. AGTR1 (C573T) and ACE (ID) association between ACE inhibitor therapy and increased MI risk for carriers of the AGTR1 C573 allele were reported; however, no significant interaction between ACE inhibitor treatment and ACE (ID) alleles for either stroke or MI were found [28]. One research group found no associations between BP response and ACE (ID), AGTR1 (A1166C), CYP11B2 (-344 C/T), AGT (-6 A/G) [57].

After 12 weeks of treatment with irbesartan (Angiotensin II Blocker), plasma concentration of the drug was related to change in systolic BP in TT homozygotes of AGTR1 (C5245T) but not for other genotypes [58].

3. Calcium Channel Blockers (CCBs)

Drugs in this class block voltage-gated calcium channels in the heart and vasculature, thereby reducing intracellular calcium. Calcium channel blockers drugs vary in their effect on cardiac versus vascular calcium channels. CCBs fall into three subclasses: phenylalkyla-

mines, which are selective for the myocardium; dihydropyridines which mostly affecting smooth muscle and benzothiazepines with a broad range.

A few studies describe some association; three SNPs in CACNA1C had significant associations with treatment in a study of BP lowering with calcium channel blockers [59]; between CYP3A5*3 and *6 variants and verapamil treatment for BP and hypertension risk outcomes in blacks and Hispanics [60]; individuals that are homozygous for the T allele of NPPA T2238C had more favourable clinical outcomes when treated with a calcium channel blocker whereas C carriers responded better to a diuretic [32]. Beta Adrenergic Receptor 1 (BAR1) Ser49-Arg389 haplotype carriers had higher death rates than those with other haplotypes when treated with verapamil [15].

4. Anticoagulants

4.1. Warfarin

Warfarin is a widely used anticoagulant in the treatment and prevention of thrombosis. It was initially marketed as a pesticide against rats and mice and is still used for this purpose. It was approved for use as a medication in the early 1950s and is widely prescribed. Despite its common use, warfarin therapy can be associated with significant bleeding complications. Achieving a safe therapeutic response can be difficult because of warfarin's narrow therapeutic index and great individual variability in the dose required, which is mostly a consequence of individual genetic variants. This fact is well known among clinicians and the wide range, from 1 mg/day to 20 mg/day, of warfarin maintenance doses are observed across the population. To maintain a therapeutic level of anti-thrombosis and to minimise the risk of bleeding complications, warfarin therapy requires intensive monitoring via the International Normalized Ratio (INR) to guide its dosing. The INR is used to monitor the effectiveness of warfarin and measures the pathway of blood coagulation. It is used to standardize the results for a prothrombin time. INR is the ratio of a patient's prothrombin time to a control sample, raised to the power of the index value for the analytical system used.

Several factors increase the risk of over-anticoagulation: genetic polymorphisms affecting the metabolising enzymes, impaired liver function, drug interactions, congestive heart failure, diarrhoea, fever, and diets rich in vitamin K [61] [62]. Nevertheless, genetic factors and drug interactions mostly account for the risk of over-anticoagulation. Warfarin metabolism involves primarily the cytochrome P450 (CYP) enzymes. Some loss-of-function CYP2C9 and vitamin K epoxide reductase complex subunit 1 (VKORC1) polymorphisms are known to be associated with decreased enzymatic activity and as a result, with an increased risk of haemorhage. These are CYP2C9*2 (Cysl44/Ile359), CYP2C9*3 (Argl44/Leu359) and VKORC1 (-1639G>A) [63-65].

Warfarin-induced haemorrhage is an important complication of anticoagulation therapy. A review of many studies shows average yearly rates of warfarin-related bleeding as high as 0.8%, 4.9%, and 15%, for fatal, major and minor bleeding complications respectively [66].

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Vitamin K is required by proteins C and S, together with clotting factors II, VII, IX, and X, to allow assembly of the procoagulant enzyme complexes necessary to generate fibrin. Warfarin as an anticoagulant agent has the ability to interfere with the recycling of vitamin K in the liver. The pharmacologic effect of warfarin is mediated by the inhibition of vitamin K epoxide reductase complex subunit 1 (EC 1.1.4.1) [67].

Warfarin consists of (R)- and (S)-warfarin enantiomers. (R)- and (S)-warfarins differ in their relative plasma concentrations, in their antithrombotic potency and in the specific isoenzymes responsible for their metabolism. (S)-warfarin has a 3 to 5 times greater anticoagulant effect than the (R)-enantiomer and accounts for 60% to 70% of warfarin's overall anticoagulant activity. (S)-warfarin is metabolised almost exclusively by CYP2C9 [68-70].

The activity of the CYP2C9 enzyme has a significant impact on the clearance of (S)-warfarin and as a consequence on anticoagulant effect. In the presence of genetic variations where the activity of CYP2C9 is reduced, clearance of (S)-warfarin is also reduced. Activity of CYP2C9 between individuals can vary by more than 20-fold. (R)-warfarin is metabilised by multiple different CYP enzymes [71].

While several single-nucleotide polymorphisms of CYP2C9 have been reported, the CYP2C9*2 (Cysl44/Ile359) and CYP2C9*3 (Argl44/Leu359) polymorphisms have been identified as clinically relevant [72]. Both of these variants are associated with decreased enzymatic activity [24, 73-78].

Homozygous CYP2C9*3 variant genotypes have only 5% to 10% metabolic efficiency compared to the wild-type genotype. As a result, compared to wild-type CYP2C9*1*1 controls, enzyme activity and the median maintenance warfarin dose for CYP2C9*3*1 heterozygotes was reduced by 40%, and by approximately 90% for CYP2C9*3*3 homozygotes [72-74].

Furuya [79] and Steward [75] showed that the CYP2C9*2 variant is also associated with reduced warfarin elimination. Heterozygotes demonstrate 40% and homozygotes 15% of the wild-type enzyme activity, causing dose adjustment for heterozygote CYP2C9*2 individuals down to 20% less than the standard dose.

Margaglione [76] has also demonstrated bleeding rates as high as 27.9 per 100 patient-years in carriers of CYP variants. In this study, findings were adjusted for other common variables associated with increased bleeding risk, such as increased age, drug interactions and abnormal liver function.

Several studies of the *2 and *3 CYP2C9 polymorphisms consistently show that patients with at least one CYP2C9 allele polymorphism have reduced warfarin requirements [76, 80-84]. Freeman [85] reported reduced warfarin weekly dosages for carriers of CYP2C9*2 or CYP2C9*3 alleles compared with patients who were homozygous for the wild-type allele (0.307 mg/kg/wk and 0.397 mg/kg/wk, respectively). Taube [83] compared warfarin maintenance dosages in 683 patients carrying different CYP2C9 genotypes. Mean warfarin maintenance dosages were 86% in patients with CYP2C9*1*2, 79% in patients with CYP2C9*1*3, 82% in compound heterozygotes CYP2C9*2/*3, and 61% in patients homozygous for CYP2C9*2. Furthermore, Aithal [80] warns that even when warfarin dosages are decreased,

carriers of CYP2C9 poor metaboliser alleles experience a rate of major bleeding that is 3.68-fold higher than the rate seen in patients with the wild type genotype.

The frequency of CYP2C9 alleles is ethnically related [82, 86]. Approximately 20% of the Caucasian population carries one of the loss-of-function CYP2C9 alleles, and it is estimated that 1% of Caucasian carry two such alleles [71]. The frequency of the CYP2C9*2 allele reportedly ranges from 8-13% in different Caucasian populations. CYP2C9*2 is present in 4% of African-Americans and is rare among Japanese individuals [87, 88]. The frequency of CYP2C9*3 is 6-10% among Caucasian populations and 3.8% in Japanese populations [88, 89]. This data suggests that a substantial fraction of the Caucasian patient population may carry at least one defective CYP2C9 allele. In this group, the usual prescription dosage of warfarin may lead to major or even life-threatening haemorrhage.

Warfarin is commonly prescribed in combination with selective serotonin reuptake inhibitors (SSRIs), as depression often coexists with cardiovascular disease. Case reports suggest that some SSRIs can interact with warfarin to increase the likelihood of bleeding [90]. SSRIs cause adverse effects in isolation [91, 92] and can interact with other medications by inhibiting various isoenzymes of the CYP450 enzyme group [93, 94]. It has been shown that metronidazole and cimetadine increase the prothrombin time in patients on warfarin therapy. Chloramphenicol enhances warfarin's effect by inhibiting the action of the hepatic P450 system [71]. Some authors [95], [96] have warned that antidepressants with a known or predictable interaction with warfarin, such as fluoxetine and fluvoxamine, should be avoided in patients receiving warfarin because of the risk of adverse outcomes.

Drug-drug interaction is a main concern in adverse drug reactions. The primary complication occurring with warfarin treatment is bleeding. SSRIs may increase the risk of bleeding during warfarin therapy by hindering platelet aggregation through depletion of platelet serotonin levels [97-99]. Some SSRIs may also inhibit the oxidative metabolism of warfarin by CYP 2C9 [95].

It has been shown that concurrent use of selective serotonin reuptake inhibitors and warfarin increases the risk of hospitalisation due to haemorrhage [90, 98]. Drugs which affect serotonin may have a detrimental effect on platelet function, as drugs which inhibit the reuptake of serotonin may decrease platelet serotonin levels leading to a reduction in serotonin-mediated platelet aggregation. Potential drug interactions can involve modification in either of these mechanisms and may result in pharmacodynamic interference or enhancement of warfarin's action.

It was shown that major and moderate drug-drug interactions with warfarin are very common in inpatients and are associated with INR results outside the therapeutic range. The most common drugs involved in the increase of anticoagulation effect were enoxaparin, simvastatin, omeprazole and tramadol. Multivariate analysis showed that age, length of hospital stay, exposure to >/=4 major or moderate drug interactions, and refusal of pharmacist recommendations contribute significantly to the patient's INR result >5 [100].

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One study demonstrated that acetaminophen, at 2 g/day or 3 g/day, enhanced the anticoagulant effect of warfarin in stable patients, thus requiring close INR monitoring in the clinical setting [101].

4.2. Heparin

One of the preventative treatments of thromboembolic disease in patients is a prescription of heparin. However, heparin induced thrombocytopenia (HIT) is one of the most serious adverse reactions. HIT consequences can include thromboembolic complications and death.

An association between the Fc receptor gene and the risk for HIT has been found in some studies and it was demonstrated that the homozygous 131Arg/Arg genotype occurred significantly more often in patients with HIT than in the healthy volunteers' group [102] [103] ; however, another group have found no association [104]. Results are very preliminary and more evidence are needed before it may be possible to genotype candidates for heparin therapy to identify those at risk for drug-induced thromboembolic complications.

5. Statins

Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) have reduced coronary and cerebrovascular events and overall mortality when used for both primary and secondary prevention of ischemic heart disease [105]. Several known gene polymorphisms are associated with the treatment progress [106, 107].

Some studies examined polymorphism in the gene encoding cholesteryl ester transfer protein (CETP), which is involved in the metabolism of high-density lipoprotein (HDL). Pravastatin-treated patients with either the B1/B1 or B1/B2 genotype (B1 presence and B2 absence of polymorphism) had significantly less atherosclerotic progression than patients receiving a placebo. Placebo-treated patients with the B2/B2 genotype had the least progression. However, pravastatin-treated patients with the B2/B2 genotype (16% of the study population) derived no benefit from pravastatin [108, 109].

The substitution (-455G/A) of the fibrinogen gene was found to be associated with an increased risk of myocardial infarction and stroke. During follow-up, placebo-treated patients homozygous for the -455A genotype had the greatest disease progression; although, no association was found with benefit in disease progression in patients on pravastatin therapy [110].

A five year study of pravastatin therapy in patients with a history of myocardial infarction and hypercholesterolemia showed that the largest benefit of pravastatin treatment in reducing these events occurred in patients with the platelet GP IIIa PlA1/A2 genotype who also carried at least one D allele of the ACE gene [111, 112].

An effect of polymorphism in the alloprotein gene was found on simvastatin therapy in a Scandinavian study. Among patients who received the placebo and had at least one apolipo-

protein e4 allele, the relative risk of death from all causes was higher than in simastatin patients with the same polymorphism [113]. This study demonstrates the potential clinical value of the alloprotein APOE genotype as a robust marker for low-density lipoprotein (LDL) responses to statin drugs, which might contribute to the identification of a particularly drug-resistant subgroup of patients [114].

Genetic variants in CYP3A4, which metabolises simvastatin, atorvastatin and lovastatin, have been associated with variability in statin efficacy. Both a nonsynonymous polymorphism (M445T) as well the CYP3A4*4 haplotype have been associated with lower LDL cholesterol levels with atorvastatin. However, in carriers of either a CYP3A4 promoter polymorphism (A290G) or the CYP3A4*1G haplotype the lipid-lowering effect of statins is not demonstrated [115-117].

Variation in Hydroxymethylglutaryl-coenzyme A reductase (HMGCR) and low-density lipoprotein receptor (LDLR) genes are associated with the LDL-lowering effect of statins. The H7 haplotype within HMGCR, defined by the presence of three intronic SNPs, has been associated with an 11% to 19% reduction in LDL cholesterol with statin treatment in multiple independent populations as well as ethnically diverse population-based cohorts [107, 114, 118]. The H7 haplotype has been shown to interact with other genetic variants, including a second HMGCR haplotype, H2, as well as the LDLR L5 haplotype, defined by six SNPs within the LDLR 3′ untranslated region. Ethnic variations in LDL cholesterol-lowering with statin treatment is also demonstrated in African-Americans who carry multiple copies of these haplotypes versus any haplotype alone [106, 118, 119].

Statin-related myotoxicity, especially rhabdomyolysis, is the subject of medical concerns as it requires changes in medications and treatment discontinuation. It was found that variants in CYP3A5 and solute carrier organic anion transporter family (SLCO1B1) gene can be potential predictors of myotoxicity [120-123].

Increased risk of coronary artery disease, coronary heart disease and myocardial infarction are associated in some studies with a missense SNP, Trp719Arg, in the KIF6 gene (kinesin family member 6). Statin treatment significantly reduce coronary events in carriers of Trp719Arg, and SNPs in high linkage disequilibrium with it, whereas no benefit of statin treatment is reported in noncarriers [124].

The differences in drug-drug interaction profiles among available statins offer the possibility of reducing the risk of myotoxicity among high-risk patients. The risk of developing the rhabdomyolysis condition with statin therapy increases at higher therapeutic doses. This effect is increased by combination with certain other medications due to drug-drug interactions. Co-administration of drugs that inhibit the cytochrome P450 (CYP) enzymes responsible for metabolizing statins, or that interact with the organic anion-transporting polypeptides (OATPs) responsible for statin uptake into hepatocytes, substantially increases the risk of developing myotoxicity. Pitavastatin, a novel statin approved for the treatment of hypercholesterolemia and combined (mixed) dyslipidemia, is not catabolized by CYP3A4, unlike other lipophilic statins, and may be less dependent on the OATP1B1 transporter for its uptake into hepatocytes before clearance [125].

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6. Antiarrhythmic

Many antiarrhythmic agents have antagonistic effects on sodium ion and potassium ion channels in the heart. A risk of proarrhythmic effects of antiarrhythmic drugs and its mechanism is associated with genetic variations. Some evidence indicates 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 [126].

The fact that the risk of drug-induced arrhythmia usually increases with increasing drug concentrations also indicates the involvement of liver enzyme polymorphisms. The CYP2D6 gene regulates cytochrome P450 metabolic pathways and some evidence shows an association between poor metaboliser phenotype and antiarrhythmic drug toxicity {127}.

A number of polymorphisms in the N-acetyltransferace 2 gene contribute to different acetylator phenotypes. Rapid acetylators have increased conversion of procainamide by N-acetyltransferase 2 to N-acetylprocainamide (NAPA) consequently leading to the QT-interval prolongation, and life-threatening ventricular arrhythmias. Slow acetylators will attain an increased concentration of procainamide levels with normal procainamide dosages, which can lead to a procainamide- induced lupus-like syndrome [128].

Sotalol, dofetilide and quinidine increase the chances of QT interval prolongation, polymorphic ventricular tachycardia and torsades de pointes. Several genes encoding ion channels or function-modifying subunits were associated with these syndromes [129],[130-132].

One study suggested that a NOS1AP variant in the gene encoding an accessory protein for neuronal nitric oxide synthase, was associated with total and cardiovascular mortality during treatment with dihydropyridine calcium channel blockers. Variants in NOS1AP also have been reported to modulate the risk of arrhythmias, at equivalent QT interval durations, in patients with the congenital long QT syndrome and to modulate risk for sudden death in the general population [133-135].

7. Antiplatelet agents

7.1. Aspirin

Pharmacogenetic studies of aspirin response to date have found associations with a few genes. It was reported that PLA2 (Leu59Pro) carriers, the variant in platelet glycoprotein IIIa, have impaired aspirin responses. After seven days of aspirin therapy in healthy volunteers, plasma prothrombin fragment concentrations in bleeding-time wounds were reduced in 23 of 25 PLA1 homozygotes, compared with 9 of 15 PLA2 carriers [136]. A meta-analysis [137] of 50 polymorphisms in 11 genes reported in 31 studies with a combined sample size of 2834 subjects suggested that the common PLA1/2 polymorphism does confer aspirin resistance (odds ratio in healthy subjects=2.36; P=0.009); however, when combining both

healthy subjects and those with cardiovascular disease, the odds ratio was 1.14 (P=0.40). The PLA2 allele occurs with a frequency of approximately 15% in humans and has been associated with increased platelet activation and aggregation in vitro [138].

Associations between the PLA polymorphisms and subacute thrombosis after coronary intervention have been described in some reports [139-141] and it was shown that an increased risk of subacute thrombosis is associated with the PLA2 allele. In one study, the risk of subacute thrombosis after coronary angioplasty and stent placement was five times greater in coronary artery disease patients with the PLA2 polymorphism than in patients homozygous for the PLA1 allele, despite similar antiplatelet therapy and similar clinical, angiographic and procedural characteristics [139].

7.2. Clopidogrel

The obvious candidates for pharmacogenetic analysis are genes involved in clopidogrel metabolism. Clopidogrel is a prodrug and its active form, thiol, is formed during the biotransformation in the liver. CYP2C19, CYP3A4/5, CYP1A2, and CYP2B6 are involved in this process [142].

P2Y12 belongs to the G protein-coupled purinergic receptor for adenosine diphosphate (ADP). The P2Y12 protein is found mainly, but not exclusively, on the surface of blood platelets, and is an important regulator in blood clotting. The active clopidogrel metabolite irreversibly binds to platelet ADP P2Y12 receptors. ADP P2Y12 receptors and loss-of-function CYP2C19*2 was identified as the single major genetic determinant of biochemical response to clopidogrel, accounting for approximately 12% of the variation in ADP-stimulated platelet aggregation during drug treatment [143]. CYP2C19*2 carriers treated with clopidogrel have an increased risk for major adverse cardiovascular events compared to noncarriers and increased risks of stent thrombosis [144].

Loss-of-function CYP2C19*2 allele has been reproducibly shown to be associated with a decreased conversion of clopidogrel into its active metabolite, reduced antiplatelet effect and increased risk for cardiovascular events in patients using clopidogrel [4, 145].

The frequency of CYP2C19*2 polymorphism varies in different populations: in Caucasian, African American, and Mexicans it presence is 18% to 33% (2%–3% homozygotes) and the allele frequency is higher in Asians. The loss-of-function *3 variant is also associated with poorer response and is highly prevalent in Asians [146, 147].

P-glycoprotein, also known as multidrug resistance protein 1 (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1) or cluster of differentiation 243 (CD243), is a glycoprotein that in humans is encoded by the ABCB1 gene. ABC transporters are transmembrane proteins that utilize the energy of adenosine triphosphate hydrolysis to carry out certain biological processes including translocation of various substrates across membranes and non-transport-related processes such as translation of RNA and DNA repair. Contradicting results have been reported for variants in ABCB1 and Gln192Arg allele in paraoxonase 1, which have been implicated in clopidogrel responsiveness. These associations need further confirmation [148-150].

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8. Conclusion

Adverse drug reactions (ADRs) have been reported to be the cause for drug withdrawal after marketing, hospital admissions, death in hospitalised patients and to be the fourth leading cause of death in developed countries. The costs associated with ADRs may radically escalate the cost for healthcare.

There is an increasing use of multiple medications to treat patients with chronic illnesses. Drug-drug interactions are common and growing in frequency due to increasing numbers of medications available and the number of patients on multiple medications. The knowledge of the pharmacodynamics and pharmacokinetics of the drugs helps to avoid unintended and problematic drug interactions. Several web sites, books, and cards are available for the clinician. The web sites are updated on a regular basis and are useful tools for prescribers.

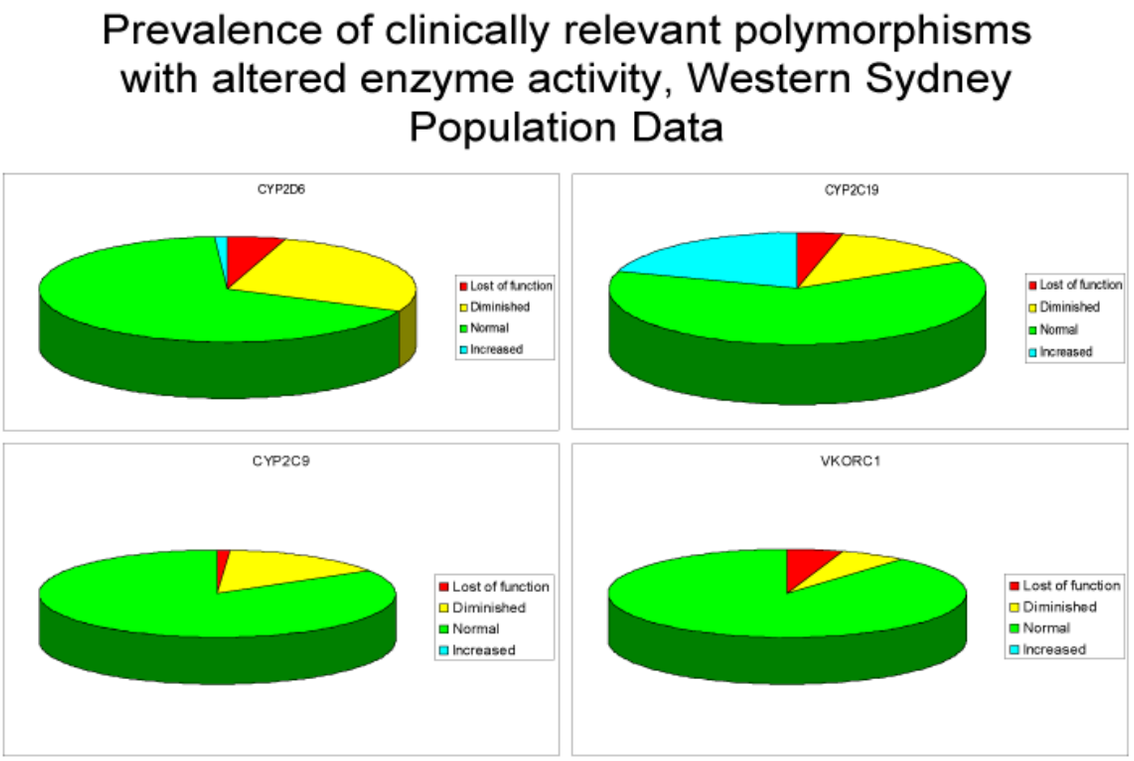
The necessity to understand drug combination pharmacokinetics and pharmacodinamics in drug interactions is illustrated by the following example: a patient who is taking a drug equally cleared by CYP2D6 and CYP3A. That patient may not be at substantial risk for toxicity when treated with either a CYP2D6 or CYP3A inhibitor alone, but may be if treated with both inhibitors at the same time [151]. Pharmacodynamic or pharmacokinetic drug interaction is a complex process and includes understanding of individual variations in drug metabolism.

Pharmacogenetics has a potential role in reducing ADRs at the pre-marketing and post-marketing stages of drug development and in clinical care. A priori identification of individuals at risk of developing ADRs for a given drug will help develop strategies to reduce the risk for ADRs in these patients. It can also be used to identify individuals at risk of developing serious ADRs and to treat these individuals with alternative therapy, thus converting ADRs that are traditionally considered unavoidable to avoidable ADRs.

Although pharmacogenetics is a highly complex and ever-evolving science, it has amassed knowledge that can readily be used to provide efficient care to patients. It has been shown that gene variants that play a role in drug metabolism pathways can alter a patient's response or increase toxicity at normal dosage range, especially in combinational drug treatments. Pharmacogenetics seeks to understand the nature of variable drug responses. Several pharmacogenetics tests are already available for cardiovascular medications in biomedical laboratories (Table 1).

Pharmacogenetic findings may help to explain ethnic differences in drug response. The accumulated facts of ethnic differences in cardiovascular drug responses and the fact that many genetic polymorphisms differ in frequency on the basis of ethnicity (example in the Western Sydney population, Fig. 1) will undoubtedly support future development of pharmacogenetics in patient care and in drug interaction interpretation.

It is possible that use of genetic and other patient-specific information, including environmental factors will help guide drug therapy decisions for certain drugs and drug combinations.



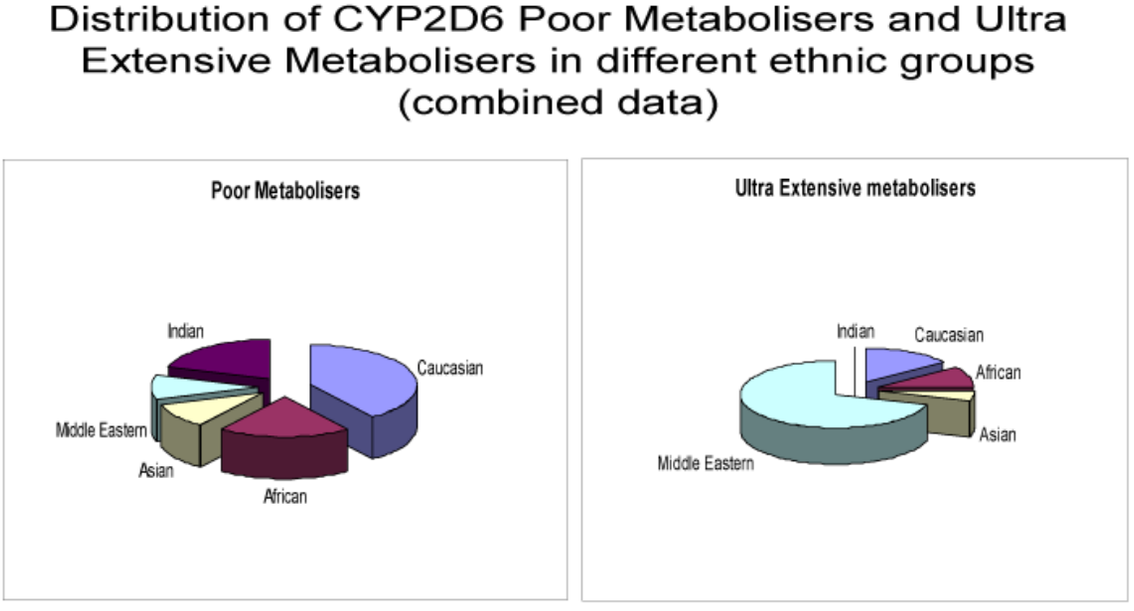


Figure 1. Example of diversity in prevalence of clinically relevant polymorphisms. (*Western Sydney Population combined data. WSLHD population is a mix of Caucasians, Asians and Africans.)

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Appendix

Glossary of some Pharmacogenetic Terms

- **Allele:** An alternative form of a gene at a given locus.
- **Genetic polymorphism:** Minor allele frequency of ≥1% in the population.
- **Genome:** The complete DNA sequence of an organism. Sum total of the genetic material included in every cell of the human body, apart from the red blood cells.
- **Genomewide association study (GWAS):** A genetic association study in which the density of genetic markers and the extent of linkage disequilibrium are sufficient to capture a large proportion of the common variation in the human genome in the population under study, and the number of specimens genotyped provides sufficient power to detect variants of modest effect.
- **Genotype:** The alleles at a specific locus an individual carries. The genetic constitution of an individual, i.e. the specific allelic makeup of an individual.
- **Haplotype:** A group of alleles from two or more loci on a chromosome; inherited as a unit.
- **Heterozygote:** A person who has two copies of an allele that are different.
- **Homozygote:** A person who has two copies of an allele that are the same.
- **Pharmacogenetics:** A study of genetic causes of individual variations in drug response. In this review, the term "pharmacogenetics" is interchangeable with "pharmacogenomics."
- **Pharmacogenomics:** Genomewide analysis of the genetic determinants of drug efficacy and toxicity. Pharmacogenetics focuses on a single gene while pharmacogenomics studies multiple genes.
- **Phenotype:** Observable expression of a particular gene or genes.
- **Single nucleotide polymorphism (SNP):** is a DNA sequence variation occurring when a single nucleotide in the genome differs between members of a biological species or paired chromosomes in an individual.

Useful Internet Resources and databases:

- OMIM (Online Mendelian Inheritance in Man), National Centre for Biotechnology Information (NCBI): www.ncbi.nlm.nih.gov/sites/entrez?db=omim
- PharmGKB (The Pharmacogenetics and Pharmacogenomics Knowledge Base): www.pharmgkb.org/#public
- NCBI, Individual SNP information, such as genetic location, nucleotide and amino acid changes, and allele frequencies in diverse populations, can be obtained from dbSNP: www.ncbi.nlm.nih.gov/sites/entrez?db=snp

- Databases: ensembl (www.ensembl.org/index.html) and HapMap (www.hapmap.org/cgi-perl/gbrowse/hapmap_B35)
- FDA: http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics
- FDA: Table of Pharmacogenomic Biomarkers in Drug Labels: http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

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