Drug Interactions, Pharmacogenomics and Cardiovascular Complication

---

Irina Piatkov, Trudi Jones and Mark McLean

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/48423>

---

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 biomarkers 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 affect β -blocker response. Therefore, drugs can compete for binding sites on the receptors or be metabolised by the same enzyme, consequently create drug-drug interaction problem.

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

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% - Intermediate, 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 β 1-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).

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 KCNB1- 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].

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 haemorrhage. These are *CYP2C9**2 (Cys144/Ile359), *CYP2C9**3 (Arg144/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].

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 metabolised by multiple different CYP enzymes [71].

While several single-nucleotide polymorphisms of CYP2C9 have been reported, the CYP2C9*2 (Cys144/Ile359) and CYP2C9*3 (Arg144/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 Caucasians 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 cimetidine 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].

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 PIA1/A2 genotype who also carried at least one D allele of the ACE gene [111, 112].

An effect of polymorphism in the apolipoprotein 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 simvastatin 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 as 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].

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-acetyltransferase 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].

Sotalolol, 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 its 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].

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 pharmacodynamics 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.

Prevalence of clinically relevant polymorphisms
with altered enzyme activity, Western Sydney
Population Data

Distribution of CYP2D6 Poor Metabolisers and Ultra
Extensive Metabolisers in different ethnic groups
(combined data)

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.)

Appendix

Glossary of some Pharmacogenetic Terms

- **Allele:** An alternative form of a gene at a given locus.
- **Genetic polymorphism:** Minor allele frequency of $\geq 1\%$ 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>

Author details

Irina Piatkov*, Trudi Jones and Mark McLean

*Address all correspondence to: irina.piatkov@swahs.health.nsw.gov.au

University of Western Sydney, Blacktown Clinical School and Research Centre,, Blacktown Hospital, Western Sydney Local Health District, Blacktown, Australia

References

- [1] Verschuren JJ, Trompet S, Wessels JA, Guchelaar HJ, de Maat MP, Simoons ML, Jukema JW (2012) A systematic review on pharmacogenetics in cardiovascular disease: is it ready for clinical application? *Eur Heart J* 33:165-175
- [2] Scheen AJ (2011) Cytochrome P450-mediated cardiovascular drug interactions. *Expert Opin Drug Metab Toxicol* 7:1065-1082
- [3] Rodriguez Arcas MJ, Garcia-Jimenez E, Martinez-Martinez F, Conesa-Zamora P (2011) Role of CYP450 in pharmacokinetics and pharmacogenetics of antihypertensive drugs. *Farm Hosp* 35:84-92
- [4] Roden DM, Johnson JA, Kimmel SE, Krauss RM, Medina MW, Shuldiner A, Wilke RA (2011) Cardiovascular pharmacogenomics. *Circ Res* 109:807-820
- [5] Masca N, Sheehan NA, Tobin MD (2011) Pharmacogenetic interactions and their potential effects on genetic analyses of blood pressure. *Stat Med* 30:769-783
- [6] Howe LA (2011) Pharmacogenomics and management of cardiovascular disease. *Nursing* 41 Suppl:1-7
- [7] PharmGKB d (2011) <http://www.pharmgkb.org/>. Stanford University
- [8] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *Jama* 289:2560-2572

- [9] Egan BM, Zhao Y, Axon RN (2010) US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. *Jama* 303:2043-2050
- [10] AHA (2008) Heart Disease and Stroke Statistics - 2008 Update. American Heart Association
- [11] Brodde OE (2008) Beta-1 and beta-2 adrenoceptor polymorphisms: functional importance, impact on cardiovascular diseases and drug responses. *Pharmacol Ther* 117:1-29
- [12] Liu J, Liu ZQ, Tan ZR, Chen XP, Wang LS, Zhou G, Zhou HH (2003) Gly389Arg polymorphism of beta1-adrenergic receptor is associated with the cardiovascular response to metoprolol. *Clin Pharmacol Ther* 74:372-379
- [13] Lanfear DE, Jones PG, Marsh S, Cresci S, McLeod HL, Spertus JA (2005) Beta2-adrenergic receptor genotype and survival among patients receiving beta-blocker therapy after an acute coronary syndrome. *Jama* 294:1526-1533
- [14] Lanfear DE, Spertus JA, McLeod HL (2006) Beta2-adrenergic receptor genotype predicts survival: implications and future directions. *J Cardiovasc Nurs* 21:474-477
- [15] Pacanowski MA, Gong Y, Cooper-Dehoff RM, Schork NJ, Shriver MD, Langae TY, Pepine CJ, Johnson JA (2008) beta-adrenergic receptor gene polymorphisms and beta-blocker treatment outcomes in hypertension. *Clin Pharmacol Ther* 84:715-721
- [16] Lemaitre RN, Heckbert SR, Sotoodehnia N, Bis JC, Smith NL, Marcianti KD, Hindorff LA, Lange LA, Lumley TS, Rice KM, Wiggins KL, Psaty BM (2008) beta1- and beta2-adrenergic receptor gene variation, beta-blocker use and risk of myocardial infarction and stroke. *Am J Hypertens* 21:290-296
- [17] Lemaitre RN, Siscovick DS, Psaty BM, Pearce RM, Raghunathan TE, Whitsel EA, Weinmann SA, Anderson GD, Lin D (2002) Inhaled beta-2 adrenergic receptor agonists and primary cardiac arrest. *Am J Med* 113:711-716
- [18] Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, Noble RJ, Packer M, Silver MA, Stevenson LW, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Jacobs AK, Hiratzka LF, Russell RO, Smith SC, Jr. (2001) ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 38:2101-2113
- [19] Marez D, Legrand M, Sabbagh N, Lo Guidice JM, Spire C, Lafitte JJ, Meyer UA, Broly F (1997) Polymorphism of the cytochrome P450 CYP2D6 gene in a European population: characterization of 48 mutations and 53 alleles, their frequencies and evolution. *Pharmacogenetics* 7:193-202

- [20] Relling MV, Cherrie J, Schell MJ, Petros WP, Meyer WH, Evans WE (1991) Lower prevalence of the debrisoquin oxidative poor metabolizer phenotype in American black versus white subjects. *Clin Pharmacol Ther* 50:308-313
- [21] Zhou HH, Wood AJ (1995) Stereoselective disposition of carvedilol is determined by CYP2D6. *Clin Pharmacol Ther* 57:518-524
- [22] Wang B, Wang J, Huang SQ, Su HH, Zhou SF (2009) Genetic Polymorphism of the Human Cytochrome P450 2C9 Gene and Its Clinical Significance. *Curr Drug Metab* 10:781-834
- [23] Beitelshes AL, Gong Y, Wang D, Schork NJ, Cooper-Dehoff RM, Langae TY, Shriver MD, Sadee W, Knot HJ, Pepine CJ, Johnson JA (2007) KCNMB1 genotype influences response to verapamil SR and adverse outcomes in the International Verapamil SR/Trandolapril Study (INVEST). *Pharmacogenet Genomics* 17:719-729
- [24] Beitelshes AL, Navare H, Wang D, Gong Y, Wessel J, Moss JI, Langae TY, Cooper-DeHoff RM, Sadee W, Pepine CJ, Schork NJ, Johnson JA (2009) CACNA1C gene polymorphisms, cardiovascular disease outcomes, and treatment response. *Circ Cardiovasc Genet* 2:362-370
- [25] Niu Y, Gong Y, Langae TY, Davis HM, Elewa H, Beitelshes AL, Moss JI, Cooper-Dehoff RM, Pepine CJ, Johnson JA (2010) Genetic variation in the beta2 subunit of the voltage-gated calcium channel and pharmacogenetic association with adverse cardiovascular outcomes in the International Verapamil SR-Trandolapril Study GENetic Substudy (INVEST-GENES). *Circ Cardiovasc Genet* 3:548-555
- [26] Sherva R, Ford CE, Eckfeldt JH, Davis BR, Boerwinkle E, Arnett DK (2011) Pharmacogenetic effect of the stromelysin (MMP3) polymorphism on stroke risk in relation to antihypertensive treatment: the genetics of hypertension associated treatment study. *Stroke* 42:330-335
- [27] Svensson-Farbom P, Wahlstrand B, Almgren P, Dahlberg J, Fava C, Kjeldsen S, Hedner T, Melander O (2011) A functional variant of the NEDD4L gene is associated with beneficial treatment response with beta-blockers and diuretics in hypertensive patients. *J Hypertens* 29:388-395
- [28] Schelleman H, Klungel OH, Wittelman JC, Breteler MM, Hofman A, van Duijn CM, de Boer A, Stricker BH (2008) Interaction between polymorphisms in the renin-angiotensin-system and angiotensin-converting enzyme inhibitor or beta-blocker use and the risk of myocardial infarction and stroke. *Pharmacogenomics J* 8:400-407
- [29] Schelleman H, Klungel OH, Wittelman JC, Breteler MM, Yazdanpanah M, Danser AH, Hofman A, van Duijn CM, de Boer A, Stricker BH (2007) Angiotensinogen M235T polymorphism and the risk of myocardial infarction and stroke among hypertensive patients on ACE-inhibitors or beta-blockers. *Eur J Hum Genet* 15:478-484
- [30] Turner ST, Bailey KR, Fridley BL, Chapman AB, Schwartz GL, Chai HS, Sicotte H, Kocher JP, Rodin AS, Boerwinkle E (2008) Genomic association analysis suggests

chromosome 12 locus influencing antihypertensive response to thiazide diuretic. Hypertension 52:359-365

- [31] Duarte JD, Turner ST, Tran B, Chapman AB, Bailey KR, Gong Y, Gums JG, Langa TY, Beitelshes AL, Cooper-Dehoff RM, Boerwinkle E, Johnson JA (2012) Association of chromosome 12 locus with antihypertensive response to hydrochlorothiazide may involve differential YEATS4 expression. *Pharmacogenomics J*
- [32] Lynch AI, Boerwinkle E, Davis BR, Ford CE, Eckfeldt JH, Leidecker-Foster C, Arnett DK (2008) Pharmacogenetic association of the NPPA T2238C genetic variant with cardiovascular disease outcomes in patients with hypertension. *Jama* 299:296-307
- [33] Hollier JM, Martin DF, Bell DM, Li JL, Chirachanchai MG, Menon DV, Leonard D, Wu X, Cooper RS, McKenzie C, Victor RG, Auchus RJ (2006) Epithelial sodium channel allele T594M is not associated with blood pressure or blood pressure response to amiloride. *Hypertension* 47:428-433
- [34] Swift PA, Macgregor GA (2004) Genetic variation in the epithelial sodium channel: a risk factor for hypertension in people of African origin. *Adv Ren Replace Ther* 11:76-86
- [35] Manunta P, Lavery G, Lanzani C, Braund PS, Simonini M, Bodycote C, Zagato L, Delli Carpini S, Tantardini C, Brioni E, Bianchi G, Samani NJ (2008) Physiological interaction between alpha-adducin and WNK1-NEDD4L pathways on sodium-related blood pressure regulation. *Hypertension* 52:366-372
- [36] Lanzani C, Citterio L, Glorioso N, Manunta P, Tripodi G, Salvi E, Carpini SD, Ferrandi M, Messaggio E, Staessen JA, Cusi D, Macciardi F, Argiolas G, Valentini G, Ferrari P, Bianchi G Adducin- and ouabain-related gene variants predict the antihypertensive activity of rosfuroxime, part 2: clinical studies. *Sci Transl Med* 2:59ra87
- [37] Vormfelde SV, Sehrt D, Bolte D, Pahl S, Tzvetkov M, Brockmoller J (2006) Hydrochlorothiazide efficacy and polymorphisms in ACE, ADD1 and GNB3 in healthy, male volunteers. *Eur J Clin Pharmacol* 62:195-201
- [38] Psaty BM, Smith NL, Heckbert SR, Vos HL, Lemaitre RN, Reiner AP, Siscovick DS, Bis J, Lumley T, Longstreth WT, Jr., Rosendaal FR (2002) Diuretic therapy, the alpha-adducin gene variant, and the risk of myocardial infarction or stroke in persons with treated hypertension. *Jama* 287:1680-1689
- [39] Davis BR, Arnett DK, Boerwinkle E, Ford CE, Leidecker-Foster C, Miller MB, Black H, Eckfeldt JH (2007) Antihypertensive therapy, the alpha-adducin polymorphism, and cardiovascular disease in high-risk hypertensive persons: the Genetics of Hypertension-Associated Treatment Study. *Pharmacogenomics J* 7:112-122
- [40] Gerhard T, Gong Y, Beitelshes AL, Mao X, Lobmeyer MT, Cooper-DeHoff RM, Langa TY, Schork NJ, Shriver MD, Pepine CJ, Johnson JA (2008) Alpha-adducin polymorphism associated with increased risk of adverse cardiovascular outcomes: results

- from GENETic Substudy of the INternational VErapamil SR-trandolapril STudy (INVEST-GENES). *Am Heart J* 156:397-404
- [41] Poch E, Gonzalez-Nunez D, Compte M, De la Sierra A (2002) G-protein beta3-subunit gene variant, blood pressure and erythrocyte sodium/lithium countertransport in essential hypertension. *Br J Biomed Sci* 59:101-104
  - [42] Brugs JJ, Isaacs A, de Maat MP, Boersma E, van Duijn CM, Akkerhuis KM, Uitterlinden AG, Witteman JC, Cambien F, Ceconi C, Remme W, Bertrand M, Ninomiya T, Harrap S, Chalmers J, Macmahon S, Fox K, Ferrari R, Simoons ML, Danser AJ (2011) A pharmacogenetic analysis of determinants of hypertension and blood pressure response to angiotensin-converting enzyme inhibitor therapy in patients with vascular disease and healthy individuals. *J Hypertens* 29:509-519
  - [43] He J, Gu D, Kelly TN, Hixson JE, Rao DC, Jaquish CE, Chen J, Zhao Q, Gu C, Huang J, Shimmin LC, Chen JC, Mu J, Ji X, Liu DP, Whelton PK (2011) Genetic variants in the renin-angiotensin-aldosterone system and blood pressure responses to potassium intake. *J Hypertens* 29:1719-1730
  - [44] Katsuya T, Iwashima Y, Sugimoto K, Motone M, Asai T, Fukuda M, Fu Y, Hatanaka Y, Ohishi M, Rakugi H, Higaki J, Ogihara T (2001) Effects of antihypertensive drugs and gene variants in the renin-angiotensin system. *Hypertens Res* 24:463-467
  - [45] Konoshita T (2011) Do genetic variants of the Renin-Angiotensin system predict blood pressure response to Renin-Angiotensin system-blocking drugs?: a systematic review of pharmacogenomics in the Renin-Angiotensin system. *Curr Hypertens Rep* 13:356-361
  - [46] Kraja AT, Hunt SC, Rao DC, Davila-Roman VG, Arnett DK, Province MA (2011) Genetics of hypertension and cardiovascular disease and their interconnected pathways: lessons from large studies. *Curr Hypertens Rep* 13:46-54
  - [47] Ceyhan K, Kadi H, Celik A, Burucu T, Koc F, Sogut E, Sahin S, Onalan O (2012) Angiotensin-converting enzyme DD polymorphism is associated with poor coronary collateral circulation in patients with coronary artery disease. *J Investig Med* 60:49-55
  - [48] Prasad A, Narayanan S, Husain S, Padder F, Waclawiw M, Epstein N, Quyyumi AA (2000) Insertion-deletion polymorphism of the ACE gene modulates reversibility of endothelial dysfunction with ACE inhibition. *Circulation* 102:35-41
  - [49] Stavroulakis GA, Makris TK, Krespi PG, Hatzizacharias AN, Gialeraki AE, Anastasiadis G, Triposkiadis P, Kyriakidis M (2000) Predicting response to chronic antihypertensive treatment with fosinopril: the role of angiotensin-converting enzyme gene polymorphism. *Cardiovasc Drugs Ther* 14:427-432
  - [50] Ohmichi N, Iwai N, Uchida Y, Shichiri G, Nakamura Y, Kinoshita M (1997) Relationship between the response to the angiotensin converting enzyme inhibitor imidapril and the angiotensin converting enzyme genotype. *Am J Hypertens* 10:951-955

- [51] O'Toole L, Stewart M, Padfield P, Channer K (1998) Effect of the insertion/deletion polymorphism of the angiotensin-converting enzyme gene on response to angiotensin-converting enzyme inhibitors in patients with heart failure. *J Cardiovasc Pharmacol* 32:988-994
- [52] Takahashi T, Yamaguchi E, Furuya K, Kawakami Y (2001) The ACE gene polymorphism and cough threshold for capsaicin after cilazapril usage. *Respir Med* 95:130-135
- [53] Schunkert H, Hense HW, Gimenez-Roqueplo AP, Stieber J, Keil U, Riegger GA, Jeunemaitre X (1997) The angiotensinogen T235 variant and the use of antihypertensive drugs in a population-based cohort. *Hypertension* 29:628-633
- [54] van Geel PP, Pinto YM, Zwinderman AH, Henning RH, van Boven AJ, Jukema JW, Bruschke AV, Kastelein JJ, van Gilst WH (2001) Increased risk for ischaemic events is related to combined RAS polymorphism. *Heart* 85:458-462
- [55] Benetos A, Topouchian J, Ricard S, Gautier S, Bonnardeaux A, Asmar R, Poirier O, Soubrier F, Safar M, Cambien F (1995) Influence of angiotensin II type 1 receptor polymorphism on aortic stiffness in never-treated hypertensive patients. *Hypertension* 26:44-47
- [56] Benetos A, Cambien F, Gautier S, Ricard S, Safar M, Laurent S, Lacolley P, Poirier O, Topouchian J, Asmar R (1996) Influence of the angiotensin II type 1 receptor gene polymorphism on the effects of perindopril and nitrendipine on arterial stiffness in hypertensive individuals. *Hypertension* 28:1081-1084
- [57] Filigheddu F, Argiolas G, Bulla E, Troffa C, Bulla P, Fadda S, Zaninello R, Degortes S, Frau F, Pitzoi S, Glorioso N (2008) Clinical variables, not RAAS polymorphisms, predict blood pressure response to ACE inhibitors in Sardinians. *Pharmacogenomics* 9:1419-1427
- [58] Kurland L, Melhus H, Karlsson J, Kahan T, Malmqvist K, Ohman KP, Nystrom F, Hagg A, Lind L (2001) Angiotensin converting enzyme gene polymorphism predicts blood pressure response to angiotensin II receptor type 1 antagonist treatment in hypertensive patients. *J Hypertens* 19:1783-1787
- [59] Bremer T, Man A, Kask K, Diamond C (2006) CACNA1C polymorphisms are associated with the efficacy of calcium channel blockers in the treatment of hypertension. *Pharmacogenomics* 7:271-279
- [60] Langaee TY, Gong Y, Yarandi HN, Katz DA, Cooper-DeHoff RM, Pepine CJ, Johnson JA (2007) Association of CYP3A5 polymorphisms with hypertension and antihypertensive response to verapamil. *Clin Pharmacol Ther* 81:386-391
- [61] Makris M, van Veen JJ, Maclean R (2010) Warfarin anticoagulation reversal: management of the asymptomatic and bleeding patient. *J Thromb Thrombolysis* 29:171-181

- [62] Watson HG, Baglin T, Laidlaw SL, Makris M, Preston FE (2001) A comparison of the efficacy and rate of response to oral and intravenous Vitamin K in reversal of over-anticoagulation with warfarin. *Br J Haematol* 115:145-149
- [63] Horne BD, Lenzini PA, Wadelius M, Jorgensen AL, Kimmel SE, Ridker PM, Eriksson N, Anderson JL, Pirmohamed M, Limdi NA, Pendleton RC, McMillin GA, Burmester JK, Kurnik D, Stein CM, Caldwell MD, Eby CS, Rane A, Lindh JD, Shin JG, Kim HS, Angchaisuksiri P, Glynn RJ, Kronquist KE, Carlquist JF, Grice GR, Barrack RL, Li J, Gage BF (2012) Pharmacogenetic warfarin dose refinements remain significantly influenced by genetic factors after one week of therapy. *Thromb Haemost* 107:232-240
- [64] Johnson JA, Gong L, Whirl-Carrillo M, Gage BF, Scott SA, Stein CM, Anderson JL, Kimmel SE, Lee MT, Pirmohamed M, Wadelius M, Klein TE, Altman RB (2011) Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. *Clinical pharmacology and therapeutics* 90:625-629
- [65] Limdi NA, Wadelius M, Cavallari L, Eriksson N, Crawford DC, Lee MT, Chen CH, Motsinger-Reif A, Sagreiya H, Liu N, Wu AH, Gage BF, Jorgensen A, Pirmohamed M, Shin JG, Suarez-Kurtz G, Kimmel SE, Johnson JA, Klein TE, Wagner MJ (2010) Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across 3 racial groups. *Blood* 115:3827-3834
- [66] Palareti G, Leali N, Coccheri S, Poggi M, Manotti C, D'Angelo A, Pengo V, Erba N, Moia M, Ciavarella N, Devoto G, Berretini M, Musolesi S (1997) [Hemorrhagic complications of oral anticoagulant therapy: results of a prospective multicenter study IS-COAT (Italian Study on Complications of Oral Anticoagulant Therapy)]. *G Ital Cardiol* 27:231-243
- [67] Hirsh J, Bates SM (2001) Clinical trials that have influenced the treatment of venous thromboembolism: a historical perspective. *Ann Intern Med* 134:409-417
- [68] Jones DR, Kim SY, Guderyon M, Yun CH, Moran JH, Miller GP (2010) Hydroxywarfarin metabolites potentially inhibit CYP2C9 metabolism of S-warfarin. *Chem Res Toxicol* 23:939-945
- [69] Kamali F, Wynne H (2010) Pharmacogenetics of warfarin. *Annu Rev Med* 61:63-75
- [70] Kaminsky LS, Zhang ZY (1997) Human P450 metabolism of warfarin. *Pharmacol Ther* 73:67-74
- [71] Adcock DM, Koftan C, Crisan D, Kiechle FL (2004) Effect of polymorphisms in the cytochrome P450 CYP2C9 gene on warfarin anticoagulation. *Arch Pathol Lab Med* 128:1360-1363
- [72] Takahashi H, Echizen H (2001) Pharmacogenetics of warfarin elimination and its clinical implications. *Clin Pharmacokinet* 40:587-603

- [73] Rettie AE, Wienkers LC, Gonzalez FJ, Trager WF, Korzekwa KR (1994) Impaired (S)-warfarin metabolism catalysed by the R144C allelic variant of CYP2C9. *Pharmacogenetics* 4:39-42
- [74] Haining RL, Hunter AP, Veronese ME, Trager WF, Rettie AE (1996) Allelic variants of human cytochrome P450 2C9: baculovirus-mediated expression, purification, structural characterization, substrate stereoselectivity, and prochiral selectivity of the wild-type and I359L mutant forms. *Arch Biochem Biophys* 333:447-458
- [75] Steward DJ, Haining RL, Henne KR, Davis G, Rushmore TH, Trager WF, Rettie AE (1997) Genetic association between sensitivity to warfarin and expression of CYP2C9*3. *Pharmacogenetics* 7:361-367
- [76] Margaglione M, Colaizzo D, D'Andrea G, Brancaccio V, Ciampa A, Grandone E, Di Minno G (2000) Genetic modulation of oral anticoagulation with warfarin. *Thromb Haemost* 84:775-778
- [77] Scordo MG, Pengo V, Spina E, Dahl ML, Gusella M, Padriani R (2002) Influence of CYP2C9 and CYP2C19 genetic polymorphisms on warfarin maintenance dose and metabolic clearance. *Clin Pharmacol Ther* 72:702-710
- [78] Visser LE, van Vliet M, van Schaik RH, Kasbergen AA, De Smet PA, Vulto AG, Hofman A, van Duijn CM, Stricker BH (2004) The risk of overanticoagulation in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon. *Pharmacogenetics* 14:27-33
- [79] Furuya H, Fernandez-Salguero P, Gregory W, Taber H, Steward A, Gonzalez FJ, Idle JR (1995) Genetic polymorphism of CYP2C9 and its effect on warfarin maintenance dose requirement in patients undergoing anticoagulation therapy. *Pharmacogenetics* 5:389-392
- [80] Aithal GP, Day CP, Kesteven PJ, Daly AK (1999) Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. *Lancet* 353:717-719
- [81] Higashi MK, Veenstra DL, Kondo LM, Wittkowsky AK, Srinouanprachanh SL, Farin FM, Rettie AE (2002) Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. *Jama* 287:1690-1698
- [82] Tabrizi AR, Zehnbauser BA, Borecki IB, McGrath SD, Buchman TG, Freeman BD (2002) The frequency and effects of cytochrome P450 (CYP) 2C9 polymorphisms in patients receiving warfarin. *J Am Coll Surg* 194:267-273
- [83] Taube J, Halsall D, Baglin T (2000) Influence of cytochrome P-450 CYP2C9 polymorphisms on warfarin sensitivity and risk of over-anticoagulation in patients on long-term treatment. *Blood* 96:1816-1819
- [84] Wadelius M, Sorlin K, Wallerman O, Karlsson J, Yue QY, Magnusson PK, Wadelius C, Melhus H (2004) Warfarin sensitivity related to CYP2C9, CYP3A5, ABCB1 (MDR1) and other factors. *Pharmacogenomics* 4:40-48

- [85] Freeman BD, Zehnbauer BA, McGrath S, Borecki I, Buchman TG (2000) Cytochrome P450 polymorphisms are associated with reduced warfarin dose. *Surgery* 128:281-285
- [86] Takahashi H, Echizen H (2003) Pharmacogenetics of CYP2C9 and interindividual variability in anticoagulant response to warfarin. *Pharmacogenomics J* 3:202-214
- [87] London SJ, Daly AK, Leathart JB, Navidi WC, Idle JR (1996) Lung cancer risk in relation to the CYP2C9*1/CYP2C9*2 genetic polymorphism among African-Americans and Caucasians in Los Angeles County, California. *Pharmacogenetics* 6:527-533
- [88] Nasu K, Kubota T, Ishizaki T (1997) Genetic analysis of CYP2C9 polymorphism in a Japanese population. *Pharmacogenetics* 7:405-409
- [89] Bhasker CR, Miners JO, Coulter S, Birkett DJ (1997) Allelic and functional variability of cytochrome P4502C9. *Pharmacogenetics* 7:51-58
- [90] Schalekamp T, Klungel OH, Souverein PC, de Boer A (2008) Increased bleeding risk with concurrent use of selective serotonin reuptake inhibitors and coumarins. *Arch Intern Med* 168:180-185
- [91] Dalton SO, Sorensen HT, Johansen C (2006) SSRIs and upper gastrointestinal bleeding: what is known and how should it influence prescribing? *CNS Drugs* 20:143-151
- [92] Meijer WE, Heerdink ER, Leufkens HG, Herings RM, Egberts AC, Nolen WA (2004) Incidence and determinants of long-term use of antidepressants. *Eur J Clin Pharmacol* 60:57-61
- [93] Greenblatt DJ, von Moltke LL, Harmatz JS, Shader RI (1998) Drug interactions with newer antidepressants: role of human cytochromes P450. *J Clin Psychiatry* 59 Suppl 15:19-27
- [94] DeVane CL (1998) Differential pharmacology of newer antidepressants. *J Clin Psychiatry* 59 Suppl 20:85-93
- [95] Duncan D, Sayal K, McConnell H, Taylor D (1998) Antidepressant interactions with warfarin. *Int Clin Psychopharmacol* 13:87-94
- [96] Sayal KS, Duncan-McConnell DA, McConnell HW, Taylor DM (2000) Psychotropic interactions with warfarin. *Acta Psychiatr Scand* 102:250-255
- [97] Hauta-Aho M, Tirkkonen T, Vahlberg T, Laine K (2009) The effect of drug interactions on bleeding risk associated with warfarin therapy in hospitalized patients. *Ann Med* 41:619-628
- [98] Wallerstedt SM, Gleeup H, Sundstrom A, Stigendal L, Ny L (2009) Risk of clinically relevant bleeding in warfarin-treated patients--influence of SSRI treatment. *Pharmacoepidemiol Drug Saf* 18:412-416
- [99] Wessinger S, Kaplan M, Choi L, Williams M, Lau C, Sharp L, Crowell MD, Keshavarzian A, Jones MP (2006) Increased use of selective serotonin reuptake inhibitors in

patients admitted with gastrointestinal haemorrhage: a multicentre retrospective analysis. *Aliment Pharmacol Ther* 23:937-944

- [100] Castro TA, Heineck I (2012) Interventions to Improve Anticoagulation With Warfarin. *Ther Drug Monit* 34:209-216
- [101] Zhang Q, Bal-dit-Sollier C, Drouet L, Simoneau G, Alvarez JC, Pruvot S, Aubourg R, Berge N, Bergmann JF, Mouly S, Mahe I (2011) Interaction between acetaminophen and warfarin in adults receiving long-term oral anticoagulants: a randomized controlled trial. *Eur J Clin Pharmacol* 67:309-314
- [102] Burgess JK, Lindeman R, Chesterman CN, Chong BH (1995) Single amino acid mutation of Fc gamma receptor is associated with the development of heparin-induced thrombocytopenia. *Br J Haematol* 91:761-766
- [103] Carlsson LE, Santoso S, Baurichter G, Kroll H, Papenberg S, Eichler P, Westerdal NA, Kiefel V, van de Winkel JG, Greinacher A (1998) Heparin-induced thrombocytopenia: new insights into the impact of the FcgammaRIIa-R-H131 polymorphism. *Blood* 92:1526-1531
- [104] Arepally G, McKenzie SE, Jiang XM, Poncz M, Cines DB (1997) Fc gamma RIIA H/R 131 polymorphism, subclass-specific IgG anti-heparin/platelet factor 4 antibodies and clinical course in patients with heparin-induced thrombocytopenia and thrombosis. *Blood* 89:370-375
- [105] Waters DD (2001) What do the statin trials tell us? *Am J Manag Care* 7:S138-143
- [106] Poduri A, Khullar M, Bahl A, Sehrawat BS, Sharma Y, Talwar KK (2010) Common variants of HMGCR, CETP, APOA1, ABCB1, CYP3A4, and CYP7A1 genes as predictors of lipid-lowering response to atorvastatin therapy. *DNA Cell Biol* 29:629-637
- [107] Chasman DI, Posada D, Subrahmanyam L, Cook NR, Stanton VP, Jr., Ridker PM (2004) Pharmacogenetic study of statin therapy and cholesterol reduction. *Jama* 291:2821-2827
- [108] Boekholdt SM, Kuivenhoven JA, Hovingh GK, Jukema JW, Kastelein JJ, van Tol A (2004) CETP gene variation: relation to lipid parameters and cardiovascular risk. *Curr Opin Lipidol* 15:393-398
- [109] Kuivenhoven JA, Hovingh GK, van Tol A, Jauhiainen M, Ehnholm C, Fruchart JC, Brinton EA, Otvos JD, Smelt AH, Brownlee A, Zwinderman AH, Hayden MR, Kastelein JJ (2003) Heterozygosity for ABCA1 gene mutations: effects on enzymes, apolipoproteins and lipoprotein particle size. *Atherosclerosis* 171:311-319
- [110] de Maat MP, Kastelein JJ, Jukema JW, Zwinderman AH, Jansen H, Groenemeier B, Bruschke AV, Kluft C (1998) -455G/A polymorphism of the beta-fibrinogen gene is associated with the progression of coronary atherosclerosis in symptomatic men: proposed role for an acute-phase reaction pattern of fibrinogen. REGRESS group. *Arterioscler Thromb Vasc Biol* 18:265-271

- [111] Bray PF, Cannon CP, Goldschmidt-Clermont P, Moya LA, Pfeffer MA, Sacks FM, Braunwald E (2001) The platelet P1(A2) and angiotensin-converting enzyme (ACE) D allele polymorphisms and the risk of recurrent events after acute myocardial infarction. *Am J Cardiol* 88:347-352
- [112] Sacks FM, Pfeffer MA, Moya LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E (1996) The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 335:1001-1009
- [113] Gerdes LU, Gerdes C, Kervinen K, Savolainen M, Klausen IC, Hansen PS, Kesaniemi YA, Faergeman O (2000) 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* 101:1366-1371
- [114] Donnelly LA, Doney AS, Dannfald J, Whitley AL, Lang CC, Morris AD, Donnan PT, Palmer CN (2008) A paucimorphic variant in the HMG-CoA reductase gene is associated with lipid-lowering response to statin treatment in diabetes: a GoDARTS study. *Pharmacogenet Genomics* 18:1021-1026
- [115] Kajinami K, Brousseau ME, Ordovas JM, Schaefer EJ (2004) CYP3A4 genotypes and plasma lipoprotein levels before and after treatment with atorvastatin in primary hypercholesterolemia. *Am J Cardiol* 93:104-107
- [116] Wang A, Yu BN, Luo CH, Tan ZR, Zhou G, Wang LS, Zhang W, Li Z, Liu J, Zhou HH (2005) Ile118Val genetic polymorphism of CYP3A4 and its effects on lipid-lowering efficacy of simvastatin in Chinese hyperlipidemic patients. *Eur J Clin Pharmacol* 60:843-848
- [117] Gao Y, Zhang LR, Fu Q (2008) CYP3A4*1G polymorphism is associated with lipid-lowering efficacy of atorvastatin but not of simvastatin. *Eur J Clin Pharmacol* 64:877-882
- [118] Krauss RM, Mangravite LM, Smith JD, Medina MW, Wang D, Guo X, Rieder MJ, Simon JA, Hulley SB, Waters D, Saad M, Williams PT, Taylor KD, Yang H, Nickerson DA, Rotter JI (2008) Variation in the 3-hydroxyl-3-methylglutaryl coenzyme A reductase gene is associated with racial differences in low-density lipoprotein cholesterol response to simvastatin treatment. *Circulation* 117:1537-1544
- [119] Mangravite LM, Wilke RA, Zhang J, Krauss RM (2008) Pharmacogenomics of statin response. *Curr Opin Mol Ther* 10:555-561
- [120] Wilke RA, Moore JH, Burmester JK (2005) Relative impact of CYP3A genotype and concomitant medication on the severity of atorvastatin-induced muscle damage. *Pharmacogenet Genomics* 15:415-421

- [121] Pasanen MK, Neuvonen M, Neuvonen PJ, Niemi M (2006) SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. *Pharmacogenet Genomics* 16:873-879
- [122] Voora D, Shah SH, Spasojevic I, Ali S, Reed CR, Salisbury BA, Ginsburg GS (2009) The SLCO1B1*5 genetic variant is associated with statin-induced side effects. *J Am Coll Cardiol* 54:1609-1616
- [123] Donnelly LA, Doney AS, Tavendale R, Lang CC, Pearson ER, Colhoun HM, McCarthy MI, Hattersley AT, Morris AD, Palmer CN (2011) Common nonsynonymous substitutions in SLCO1B1 predispose to statin intolerance in routinely treated individuals with type 2 diabetes: a go-DARTS study. *Clin Pharmacol Ther* 89:210-216
- [124] Li Y, Sabatine MS, Tong CH, Ford I, Kirchgeßner TG, Packard CJ, Robertson M, Rowland CM, Bare LA, Shepherd J, Devlin JJ, Iakoubova OA (2011) Genetic variants in the KIF6 region and coronary event reduction from statin therapy. *Hum Genet* 129:17-23
- [125] Catapano AL (2012) Statin-induced myotoxicity: pharmacokinetic differences among statins and the risk of rhabdomyolysis, with particular reference to pitavastatin. *Curr Vasc Pharmacol* 10:257-267
- [126] Priori SG, Barhanin J, Hauer RN, Haverkamp W, Jongsma HJ, Kleber AG, McKenna WJ, Roden DM, Rudy Y, Schwartz K, Schwartz PJ, Towbin JA, Wilde AM (1999) Genetic and molecular basis of cardiac arrhythmias: impact on clinical management parts I and II. *Circulation* 99:518-528
- [127] Thorn HA, Lundahl A, Schrickx JA, Dickinson PA, Lennernas H (2011) Drug metabolism of CYP3A4, CYP2C9 and CYP2D6 substrates in pigs and humans. *Eur J Pharm Sci* 43:89-98
- [128] Ylitalo P, Ruosteenoja R, Leskinen O, Metsä-Ketela T (1983) Significance of acetylator phenotype in pharmacokinetics and adverse effects of procainamide. *Eur J Clin Pharmacol* 25:791-795
- [129] Roden DM (2006) Long QT syndrome: reduced repolarization reserve and the genetic link. *J Intern Med* 259:59-69
- [130] Paulussen AD, Gilissen RA, Armstrong M, Doevendans PA, Verhasselt P, Smeets HJ, Schulze-Bahr E, Haverkamp W, Breithardt G, Cohen N, Aerssens J (2004) Genetic variations of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in drug-induced long QT syndrome patients. *J Mol Med (Berl)* 82:182-188
- [131] Yang P, Kanki H, Drolet B, Yang T, Wei J, Viswanathan PC, Hohnloser SH, Shimizu W, Schwartz PJ, Stanton M, Murray KT, Norris K, George AL, Jr., Roden DM (2002) Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. *Circulation* 105:1943-1948
- [132] Itoh H, Sakaguchi T, Ding WG, Watanabe E, Watanabe I, Nishio Y, Makiyama T, Ohno S, Akao M, Higashi Y, Zenda N, Kubota T, Mori C, Okajima K, Haruna T, Miya-

- moto A, Kawamura M, Ishida K, Nagaoka I, Oka Y, Nakazawa Y, Yao T, Jo H, Sugimoto Y, Ashihara T, Hayashi H, Ito M, Imoto K, Matsuura H, Horie M (2009) Latent genetic backgrounds and molecular pathogenesis in drug-induced long-QT syndrome. *Circ Arrhythm Electrophysiol* 2:511-523
- [133] Becker ML, Visser LE, Newton-Cheh C, Hofman A, Uitterlinden AG, Witteman JC, Stricker BH (2009) A common NOS1AP genetic polymorphism is associated with increased cardiovascular mortality in users of dihydropyridine calcium channel blockers. *Br J Clin Pharmacol* 67:61-67
- [134] Crotti L, Monti MC, Insolia R, Peljto A, Goosen A, Brink PA, Greenberg DA, Schwartz PJ, George AL, Jr. (2009) NOS1AP is a genetic modifier of the long-QT syndrome. *Circulation* 120:1657-1663
- [135] Tomas M, Napolitano C, De Giuli L, Bloise R, Subirana I, Malovini A, Bellazzi R, Arking DE, Marban E, Chakravarti A, Spooner PM, Priori SG (2010) Polymorphisms in the NOS1AP gene modulate QT interval duration and risk of arrhythmias in the long QT syndrome. *J Am Coll Cardiol* 55:2745-2752
- [136] Undas A, Sanak M, Musial J, Szczeklik A (1999) Platelet glycoprotein IIIa polymorphism, aspirin, and thrombin generation. *Lancet* 353:982-983
- [137] Goodman T, Ferro A, Sharma P (2008) Pharmacogenetics of aspirin resistance: a comprehensive systematic review. *Br J Clin Pharmacol* 66:222-232
- [138] Goodall AH, Curzen N, Panesar M, Hurd C, Knight CJ, Ouwehand WH, Fox KM (1999) Increased binding of fibrinogen to glycoprotein IIIa-proline33 (HPA-1b, PlA2, Zwb) positive platelets in patients with cardiovascular disease. *Eur Heart J* 20:742-747
- [139] Walter DH, Schachinger V, Elsner M, Dimmeler S, Zeiher AM (1997) Platelet glycoprotein IIIa polymorphisms and risk of coronary stent thrombosis. *Lancet* 350:1217-1219
- [140] Kastrati A, Koch W, Gawaz M, Mehilli J, Bottiger C, Schomig K, von Beckerath N, Schomig A (2000) PlA polymorphism of glycoprotein IIIa and risk of adverse events after coronary stent placement. *J Am Coll Cardiol* 36:84-89
- [141] Abbate R, Marcucci R, Camacho-Vanegas O, Pepe G, Gori AM, Capanni M, Simonetti I, Prisco D, Gensini GF (1998) Role of platelet glycoprotein PL(A1/A2) polymorphism in restenosis after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 82:524-525
- [142] Savi P, Nurden P, Nurden AT, Levy-Toledano S, Herbert JM (1998) Clopidogrel: a review of its mechanism of action. *Platelets* 9:251-255
- [143] Shuldiner AR, O'Connell JR, Bliden KP, Gandhi A, Ryan K, Horenstein RB, Damcott CM, Pakyz R, Tantry US, Gibson Q, Pollin TI, Post W, Parsa A, Mitchell BD, Faraday N, Herzog W, Gurbel PA (2009) Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *Jama* 302:849-857

- [144] Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, Cannon CP, Danchin N, Giusti B, Gurbel P, Horne BD, Hulot JS, Kastrati A, Montalescot G, Neumann FJ, Shen L, Sibbing D, Steg PG, Trenk D, Wiviott SD, Sabatine MS (2010) Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *Jama* 304:1821-1830
- [145] Roden DM, Stein CM (2009) Clopidogrel and the concept of high-risk pharmacokinetics. *Circulation* 119:2127-2130
- [146] Santos PC, Soares RA, Santos DB, Nascimento RM, Coelho GL, Nicolau JC, Mill JG, Krieger JE, Pereira AC (2011) CYP2C19 and ABCB1 gene polymorphisms are differently distributed according to ethnicity in the Brazilian general population. *BMC Med Genet* 12:13
- [147] Solus JF, Arietta BJ, Harris JR, Sexton DP, Steward JQ, McMunn C, Ihrie P, Mehall JM, Edwards TL, Dawson EP (2004) Genetic variation in eleven phase I drug metabolism genes in an ethnically diverse population. *Pharmacogenomics* 5:895-931
- [148] Jaitner J, Morath T, Byrne RA, Braun S, Gebhard D, Bernlochner I, Schulz S, Mehili J, Schomig A, Koch W, Kastrati A, Sibbing D (2012) No association of ABCB1 C3435T genotype with clopidogrel response or risk of stent thrombosis in patients undergoing coronary stenting. *Circ Cardiovasc Interv* 5:82-88, S81-82
- [149] Kubica A, Kozinski M, Grzesk G, Fabiszak T, Navarese EP, Goch A (2011) Genetic determinants of platelet response to clopidogrel. *J Thromb Thrombolysis* 32:459-466
- [150] Luo M, Li J, Xu X, Sun X, Sheng W (2011) ABCB1 C3435T polymorphism and risk of adverse clinical events in clopidogrel treated patients: A meta-analysis. *Thromb Res*
- [151] Preskorn SH (2003) Relating clinical trials to psychiatric practice: part I: the case of a 13-year old on aripiprazole and fluoxetine. *J Psychiatr Pract* 9:307-313