

# Pharmacogenomics: a perspective of personalized medicine in CHD treatment as a model

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Although several drug dosage algorithms are available, clinicians today still commonly use the trial and error method in discovering what medicine and in what doses will be most beneficial for each patient. There are currently still very few tools available to help solve these problems, although nowadays there is more and more evidence to show that for a number of drugs, genetic variability plays an important (and sometimes central) role in variable response to drugs.

This review is focused on the variation within the genes associated with the function of medicines from major pharmaceutical groups of drugs used for the treatment of coronary heart disease (CHD). These include anticoagulants,  $\beta$ -blockers, angiotensin-converting enzyme (ACE) inhibitors, antiarrhythmics, angiotensin II receptor blockers (ARBs), diuretics, and statins. The progress in the field of CHD pharmacogenomics, which is one of the major focuses in the field of cardiovascular medicine, is ensured by a multitude of studies generating some statistically significant findings that will quite plausibly change the way clinicians treat patients on an individual level.

Pharmacogenomic research of cardiovascular medicine in the majority of cases has provided conflicting results thus delaying the implementation of genetic testing to create genotype-based medication dosing algorithms. Nevertheless, analysis of the literature reveals that based on the pharmacogenomic research progress of warfarin and to some extent clopidogrel, the practical use of pharmacogenomics in the future is plausible.

**Key words:** pharmacogenomics, coronary heart disease, medications

## PHARMACOGENOMICS AND INDIVIDUALIZED MEDICINE

Although several drug dosage algorithms are available, clinicians today still commonly use the trial-and-error method for discovering what medicine and in what doses will be most beneficial for each patient. Healthcare professionals currently agree that the prime choice for the improvement of this system is to ensure that clinicians are able to prescribe medications based on the specific particularities of a patient. This can only be achieved by knowing in advance which medicine will work best for a specific patient (1, 2). It is currently well recognized that there is great interpa-

tient variability in response to drugs, including drugs used in the treatment of cardiovascular diseases. There are many factors that can contribute to the way a patient responds to a certain drug, such as race, age, sex, body constitution, nutrition, organ function, diseases, concomitant medications, and genetic factors (3). Therefore, while certain patients may attain the desired therapeutic effect from a given drug, others may not only show no therapeutic benefit, but also experience adverse drug reactions. There are currently still very few tools available to help solve these problems, although nowadays there is more and more evidence being accumulated to show that for a number of drugs, genetic variability plays an important (and sometimes central) role in variable response to drugs. The fields of pharmacogenetics and pharmacogenomics are focused on providing knowledge of the genetic contribution to variable drug response.

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Cardiovascular disease (CVD) is the number one cause of death in Europe and the United States of America, the coronary heart disease (CHD) or coronary artery disease (CAD) being the most common type of heart disease which is caused by the hardening and narrowing of the coronary arteries (4). The progress in the field of CHD pharmacogenomics, which is one of the major focuses in the field of cardiovascular medicine, is ensured by a multitude of studies generating some statistically significant findings that will quite plausibly change the way clinicians treat patients on an individual level.

This review is focused on the variation within the genes associated with the function of medicines from major pharmaceutical groups of drugs used for the treatment of CHD. These include anticoagulants,  $\beta$ -blockers, angiotensin-converting enzyme (ACE) inhibitors, antiarrhythmics, angiotensin II receptor blockers (ARBs), diuretics, and statins. As the development and progression of CHD are influenced by various preexisting conditions (hypertension, obesity, hyperlipidemia, etc.), it is important to note that the medications and medication groups described in this review are used in the treatment of various other cardiovascular diseases, and not all reviewed medications are used in the treatment of every patient diagnosed with CHD.

## PHARMACOGENOMICS OF ANTITHROMBOTICS

Warfarin and other coumarin-based anticoagulants are the most widely used oral anticoagulant agents worldwide, but the appropriate dose of warfarin is difficult to establish because it can have a tenfold variation between patients, while an administration of an incorrect dose may lead to fatal consequences. It is for these reasons that a lot of effort is being made to find the novel ways of determining the proper doses of warfarin needed by a specific patient (4).

While the factors such as age and body constitution together with clinical factors of each particular case, have been used for a long time, it is now widely agreed that genetic variations in two genes – cytochrome P450, family 2, subfamily C, polypeptide 9 (*CYP2C9*), and vitamin K epoxide reductase complex, subunit 1 (*VKORC1*) – contribute significantly to the variability of warfarin dose requirements in different patients (5–7).

The algorithms proposed for selecting the optimal warfarin dose are usually based on relatively small clinical populations, thus rendering their results unreliable when considering their use in clinical settings (2, 8–10). Although there are ongoing large-scale studies in both the United States and Europe, which might provide healthcare specialists with estimation of the actual usability of the warfarin dosage algorithms.

The metabolism of coumarin-based anticoagulants and warfarin in particular, which affects platelet aggregation by inhibiting the enzyme vitamin K epoxide reductase, which in turn reduces vitamin K after its oxidation in the gamma glutamyl carboxylase reaction, is well understood. The inhibition reaction takes place during the normal activation of clotting factors in the coagulation cascade (9). Warfarin is a racemic mixture of R and S enantiomers, the S enantiomer being about three times more potent than the R enantiomer. The *CYP2C9* enzyme, which is a member of the cytochrome P450 superfamily, is important in the metabolism and inactivation of the S-warfarin. Polymorphisms within the *CYP2C9* gene cause the expression of proteins with different catalytic activities. The wild-type allele of the *CYP2C9* gene is denoted as *CYP2C9*\*1, while the two most common variants are the *CYP2C9*\*2 allele, which has an Arg144Cys substitution, and the *CYP2C9*\*3 allele, which has an Ile359-Leu substitution. About 20% of the Caucasian population are heterozygous (\*1\*2) and 2% are homozygous (\*2\*2) for *CYP2C9*\*2 genotype. A smaller proportion of the population is homozygous (\*3\*3) or heterozygous (\*1\*3 or \*2\*3) for the \*3 genotype. Studies have shown that the above-mentioned *CYP2C9* gene variants are associated with a decreased metabolism of S-warfarin *in vitro*; for the \*2 genotype, enzyme activity decreases by 30%, and for \*3 it decreases by 80%. The polymorphism within the *CYP2C9* gene, which has a major role in the phase I metabolism of coumarin anticoagulants, affects its activity, and the fact that these polymorphisms contribute to individual anticoagulant dose requirement is well known.

Another gene with a well-established effect on warfarin coagulation is *VKORC1* which encodes the enzyme vitamin K epoxide reductase (10). Although the gene was identified relatively recently, it has already been proven that the polymorphism in this gene's non-coding sequences affects the levels of gene expression. This variation in gene expression levels causes differences in the amounts of the enzyme in the hepatocytes of patients (11). Through the investigation of several European populations it has been shown that the alleles of the G-1639A polymorphism (located upstream from the transcription site) cause differences in gene expression, whereas the G allele (more common in Europeans) causes a higher expression than does the A allele (12, 13). The VKOR protein levels seem to affect the required dose of the anticoagulant. A clear association between the G-1639A polymorphism and warfarin dose requirement has been reported in many independent studies (10, 11, 14), with other coumarin-derived anticoagulants (acenocoumarol and phenprocoumon) showing similar associations (12).

Some studies have also identified a contribution to warfarin dose requirements from another cytochrome P450 peptide encoded by the *CYP4F2* gene. In a study in

which an Affymetrix ADME gene chip was used, SNP in *CYP4F2*, which causes the amino acid change V433M, was determined to be associated with warfarin dose requirement (15). The effect of the *CYP4F2* genotype on warfarin dosing was observed in three independent populations, to show that the patients homozygous for the variant (T) allele had a higher warfarin dose requirements compared to the patients homozygous for the wild-type (C) allele. Similar results were demonstrated by a genome wide association study (16). Although many studies have confirmed an association of the *CYP4F2* polymorphism with warfarin dosage requirements, the actual biological pathway through which the enzyme affects warfarin metabolism is largely unknown. The role of the functionally significant *CYP4F2* V433M polymorphism in eicosanoid metabolism through the production of 20-hydroxyeicosatetraenoic acid is well known, with the 433M variant decreasing its activity. However, its direct effect on warfarin or vitamin K metabolism remains unclear (15). The results of the studies that have investigated the contribution of the *CYP4F2* gene polymorphisms on the warfarin dose variation show that *CYP4F2* polymorphisms make an overall contribution of only about 1–2%; thus, the possibility of the *CYP4F2* genotype testing in clinical practice remains doubtful (15).

Clopidogrel has become one of the most commonly used oral antiplatelet agents for the treatment of CHD as well as other atherosclerotic diseases. It is often used as a stand-alone drug for the prevention of myocardial infarction (MI) in high-risk patients (e. g., patients with a history of MI, stroke, or peripheral artery disease), as well as for the secondary prevention of strokes. Clopidogrel has achieved this usage popularity despite its well-known interpatient response variability as in some cases it fails to prevent acute thrombotic events. This lack of response uniformity led to the development of the term “clopidogrel resistance”. One of the causing factors leading to the failure of clopidogrel to produce a therapeutic effect is genetic variation in some of the genes involved in the metabolism of clopidogrel. In randomized controlled trials, approximately 9% of patients undergoing percutaneous coronary intervention (PCI), who receive both clopidogrel and aspirin, still have an incidence of cardiovascular death, MI, or stroke the next year.

There is a multitude of genes the products of which are involved in the absorption and activation of clopidogrel (*CYP3A4*, *CYP3A5*, *CYP1A2*, *CYP2B6*, *P2RY12* and *ITGB3*), although these have shown little or no association with the organisms response to clopidogrel treatment (17), whereas variants of three other genes, the products of which are involved in clopidogrel metabolism (*CYP2C19*, *ABCB1* and *PON1*), have suggested a potentially significant impact on clopidogrel efficacy.

Currently, there are over 20 allelic variants of *CYP2C19* identified. The wild-type allele is denoted *CYP2C19\*1*. There

are both non-functional and gain-of-function alleles. The most common nonfunctional alleles include *CYP2C19\*2*, and *CYP2C19\*3*, while the recently discovered *CYP2C19\*17* has been reported as a gain-of-function allele causing an increased enzymatic activity. The *CYP2C19\*17* allelic variant is located upstream of the coding region and is thought to increase the efficiency of gene transcription. All of these alleles display a considerable inter-ethnic variation.

The *ABCB1* (ATP-binding cassette B1) gene encodes the efflux pump, P-glycoprotein, also known as MDR1 (multi-drug resistance 1 protein). *ABCB1* is a member of the transporter gene family, all of which have a broad substrate specificity. Transporter gene products act to protect the organism from a wide range of xenobiotics. In some pathological conditions, these genes can have a negative impact on the body as is the case in certain cancer patients in which these genes are overexpressed, causing chemotherapeutic agent resistance.

In recent studies that used *in vitro* metabolomic profiling techniques, esterase paraoxonase-1 (*PON1*) was identified as the crucial enzyme for clopidogrel bioactivation by the hydrolytic cleavage of the  $\gamma$ -thiobutylolactone ring. The Arg192 allozyme created by a SNP Q192R in the *PON1* gene, compared with the Gln192 allozyme, showed a higher hydrolysis efficiency for 2-oxo-clopidogrel. In a recent research, a group of individuals with coronary artery disease, who had undergone stent implantation and received clopidogrel therapy, were investigated. It was found that *PON1* QQ192 homozygous individuals showed a considerably higher risk than RR192 homozygous individuals of stent thrombosis, a lower *PON1* plasma activity, lower plasma concentrations of active metabolite and a lower platelet inhibition. Although not all studies into the importance of the *PON1* gene for the bioactivation of clopidogrel are in concordance, there are some results that show the potential of *PON1* Q192R genotyping to be used in clinical settings (18).

For many years aspirin has been a standard therapy in patients who are at a high risk of ischemic heart disease or stroke. It is often used in combination with clopidogrel for a dual antiplatelet therapy after percutaneous coronary intervention (PCI) and for preventing recurring acute coronary events in patients with recent stent placement or a recent acute coronary syndrome. Aspirin exhibits its antiplatelet effect by inhibiting cyclooxygenase-1 (*COX-1*) which is responsible for the production of thromboxane A<sub>2</sub> (TXA<sub>2</sub>). TXA<sub>2</sub> promotes platelet activation and subsequently platelet aggregation, whereas the failure of aspirin to inhibit platelet aggregation could be called aspirin resistance (18, 19).

Polymorphisms within the *COX-1* encoding (*PTGS1*) gene and specifically the A-842G polymorphism in the promoter region, which is in complete linkage disequilibrium with C50T polymorphism, are associated with a decreased

response to aspirin treatment, although other researchers have published contradictory results (20). Another gene whose polymorphisms may also be associated with aspirin resistance is *ITGB3* which encodes the glycoprotein IIIA (GPIIIA) receptor. Research has identified the Leu33Pro SNP in the second exon of the *ITGB3* gene to be associated with increased platelet activation and aggregation and thus with an increased risk of stent thrombosis after PCI and other adverse cardiovascular outcomes. The results of association studies of the *ITGB3* gene have proven to be inconsistent as other researchers have found no association with the published converse findings. It should be noted that these studies have used different populations and methods to confirm the association, and therefore more uniform research is required to confirm or dismiss the association and implement genetic testing to determine aspirin dosage (21).

## PHARMACOGENOMICS OF STATINS

Currently, a variety of lipid-lowering drugs are in use. Plasma cholesterol and lipids are a major cause of plaque build-up and atheroma formation in coronary arteries. This process eventually leads to the development of atherosclerosis and CHD. Statins are particularly well-suited for lowering the low-density lipoprotein cholesterol (LDL-C) which has the strongest links with cardiovascular diseases. In studies using standard doses, statins have been found to lower LDL-C by 18% to 55%, depending on the specific statin being used. Notably, there is a risk of severe muscular damage (myopathy & rhabdomyolysis) for patients prescribed with statin therapy. The variation of response to treatment, together with severe drug-induced side effects, makes statins a primary target for pharmacogenomic research.

3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are a class of medications that lower cholesterol levels by decreasing cholesterol production in the liver (22). Statins are routinely used in clinical practice for CHD prevention (24). Inhibiting the biosynthesis of cholesterol reduces the secretion of apolipoprotein B (APOB) and upregulates the LDL receptor activity, thus lowering cholesterol in plasma (22). The variation in response to statin therapy in CHD patients is now thought to be, at least partially, caused by genetic factors (25, 26). Cholesterol metabolism in the human organism is carried out through a complex pathway with many factors contributing to its synthesis, transport and removal; therefore, unsurprisingly, many candidate genes were explored in relation to statin efficacy and toxicity (22). These multiple studies produced some interesting results, although the lack of follow-up studies prevents the formation of guideline genetic tests for the use in clinical practice.

In the pharmacogenomic research of lipid-lowering medications, polymorphisms within the apolipoprotein E gene (*APOE*) have probably been most extensively studied (8). A combination of two common polymorphisms in the *APOE* gene, causing amino acid changes (Cys112Arg and Cys158Arg), results in ApoE isoforms:  $\epsilon 2$  (Cys112; Cys158),  $\epsilon 3$  (wild-type; Cys112; Arg158) and  $\epsilon 4$  (Arg112; Arg158) (22, 25, 27). ApoE has multiple functions in lipid metabolism. ApoE binds to LDL-receptor (LDLR) and mediates the uptake of chylomicrons, very low-density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL). The genetic variation of *APOE* may modify its activity and consequently affect cholesterol and triglyceride levels (25). There have been a few studies to show that when treated with statins for lipid lowering, patients with the  $\epsilon 4$  isoform of ApoE show the lowest response to statins, patients with  $\epsilon 2$  isoform showed the strongest one, the wild-type *APOE* carrying patients falling somewhere in the middle. The treatment of ApoE  $\epsilon 2$  patients with statins is therefore more likely to achieve therapeutic LDL lowering goals. The results of ApoE isoforms' effect on the function of statins mirror the effect of the isoforms on the development of atherosclerosis and CHD. ApoE  $\epsilon 4$  carriers are at the highest risk of CHD,  $\epsilon 2$  causes the lowest risk of CHD, and  $\epsilon 3$  carriers are inbetween (22, 25). The *LDLR* gene has been the focus of some pharmacogenomic studies because of their role in cholesterol binding and metabolism. A synonymous SNP c.1773C > T within exon 12 of the *LDLR* gene has been associated with an increase in LDL cholesterol in women (28).

Genes in the CYP450 gene family are prime candidates to be looked at with regard to statin metabolism as widely used medications like atorvastatin, pravastatin and simvastatin were shown to be metabolized by CYP3A4, and fluvastatin by CYP2C9. The metabolism of other statin medications, such as pravastatin and rosuvastatin, do not appear to be metabolized by the CYP450 system. Other CYP450 family genes were also identified as candidates as in one study it was determined that lovastatin was considerably more effective in patients who had a normal *CYP3A5* gene expression as compared with patients who lacked CYP3A4 (22).

Permeability glycoprotein (P-glycoprotein), known also as P-gly, multidrug resistance-1 (*MDR1*) gene or ATP-binding cassette transporter (ABC), is encoded by the *ABCB1* gene and has been found to affect drug disposition. Several ABC subfamily genes, including *ABCG5* and *ABCG8*, have been studied to explain the variation of statin effect in patients. The *ABCG8* gene Asp19His polymorphism in particular was associated with a greater reduction in LDL when treated with atorvastatin (29). The Asp19His polymorphism was also associated with a reduction in intestinal cholesterol absorption (22, 24).

Statin therapy is designed for HMG-CoA reductase inhibition; therefore, polymorphisms within the *HMGCR* gene have naturally been in the focus of several studies. One study showed a significant association between *HMGCR* SNP 12 (rs17244841) and 29 (rs17238540), both located on chromosome 5 and being in a tight linkage disequilibrium ( $r^2 > 0.9$ ), with a reduced efficacy of pravastatin therapy. Individuals homozygous for the minor allele in one of the SNPs (T allele in SNP 12 and G allele in SNP 29) had a 22% and 19% smaller reduction in total cholesterol and LDL, respectively, compared to heterozygous carriers (29).

Different statin medications have distinct metabolic pathways; therefore, more extensive studies are required on other popular statins utilized in medical practice (22). *APOE* and *HMGCR*, as well as some CYP450 family genes, seem to show the most promising data; however, more large-scale studies are needed to use their genotyping in clinical practice (25, 29).

## PHARMACOGENOMICS OF $\beta$ -BLOCKERS

$\beta$ -blockers, widely adopted in the treatment of cardiovascular diseases and CHD in particular have shown to be promising in the treatment of hypertension, heart failure (HF) and MI (9).  $\beta$ -blockers block the effects of norepinephrine and epinephrine by antagonizing  $\beta_1$  and  $\beta_2$  adrenergic receptors (*ADRB1* and *ADRB2*, respectively) to slow nerve impulses and decrease the workload of the heart (30). Several classes of  $\beta$ -blockers are described depending on their mode of action. These include selective and nonselective  $\beta$ -blockers and the ones that block just  $\beta$  receptors or both  $\beta$  and  $\alpha$  receptors. *ADRB1* Ser49Gly and Arg389Gly polymorphisms have been shown to possibly affect receptor function, while Gly16Arg and Gln27Glu polymorphisms seem to have an effect on *ADRB2* function (9).

The majority of  $\beta$ -blocker pharmacogenomic studies are concentrated on *ADRB1* (31). Some studies have

Table 1. Genes and polymorphisms associated with medications for CHD treatment

Class of medications	Examples of medications	Associated genes	Gene product function	Important polymorphism	Effect of polymorphism
Antithrombotics	Warfarin Aspirin Clopidogrel	CYP2C9	Phase I metabolism of xenobiotics	Arg144Cys	Decrease enzymatic activity by 30%
				Ile359Leu	Decrease enzymatic activity by 80%
		VKORC1	Enzymatically activated form of vitamin K	G-1639A	Increased expression
		CYP4F2	Phase I metabolism of xenobiotics	Val433Met	Reduced metabolic rate
		CYP2C19	Phase I metabolism of xenobiotics	CYP2C19*2	Non-functional enzyme
				CYP2C19*3	Non-functional enzyme
		CYP2C19*17	Increased enzymatic activity		
		PTGS1	Catalyzes the metabolism of arachidonic acid to prostaglandin H(2)	A-842G C50T	Reduced level of COX-1
$\beta$ -blockers	Propranolol Carvedilol	ADRB1	Mediates the physiological effects of epinephrine and norepinephrine	Ser49Gly	Decreased heart rate
				Arg389Gly	Lower response to $\beta$ -blocker treatment
ACE inhibitors	Perindopril Enalapril	AGT	Precursor of angiotensin II	Met235Thr	Higher circulating levels of angiotensin
Diuretics	Indapamide	ADD1	Promotes the assembly of the spectrin-actin network	Gly460Trp	Greater reduction of blood pressure by thiazide diuretics
		NPPA	Regulation of natriuresis, diuresis, and vasodilatation	T2238C	Decreased CHD event rates and bp* after chlorthalidone treatment
Statins	Atorvastatin Fluvastatin Rosuvastatin	APOE	Mediates the binding, internalization, and catabolism of lipoprotein particles	<i>APOE</i> $\epsilon$ 2	High response to statin treatment
				<i>APOE</i> $\epsilon$ 4	Low response to statin treatment
		LDLR	Transports LDL into cells by endocytosis	c.1773C > T	Increase in LDL cholesterol
		ABCG8	Transport of the dietary cholesterol in and out of the enterocytes and selective sterol excretion by the liver into bile	Asp19His	Greater reduction in LDL after atorvastatin treatment
		HMGCR	Rate-limiting enzyme of sterol biosynthesis	SNP 12	T allele smaller reduction of LDL and total cholesterol
				SNP 29	G allele smaller reduction of LDL and total cholesterol

\* bp – blood pressure.

identified that patients carrying the 389Arg allele exhibit a greater overall response to  $\beta$ -blocker treatment as compared with the 389Gly allele carriers. The 389Arg allele has been found to show significant improvements in left ventricular ejection fraction (LVEF) in response to  $\beta$ -blockers, together with larger reductions in heart rate, blood pressure and a significant overall decrease in hospitalizations and mortality compared to the Gly389 carriers (9, 32, 33).

*ADRB1* Ser49Gly polymorphism Gly49 allele has been associated with greater reductions in the end diastolic diameter as compared with the 49Ser allele. The 49Ser genotype has also been associated with an increase in heart rate and an overall increase in mortality as compared with Gly49 carriers treated with  $\beta$ -blockers (9).

Inconclusive results have been demonstrated in a few studies that reviewed the *ADRB2* Gly16Arg and Gin27Glu polymorphisms (31). The 27Gin and 16Arg genotypes have been associated with overall increases in mortality in patients receiving  $\beta$ -blockers as compared with the 27Glu and 16Gly carriers. As there have been many inconclusive and a few studies to show results converse to those mentioned above, it has to be said that more research need to be carried out with adrenergic receptor gene polymorphisms to find the gene variants with the most pronounced influence on  $\beta$ -blocker function. Another area of interest, which has not been explored in sufficient depth, is the effect of polymorphisms in the cytochrome P450 enzyme coding genes and *CYP2D6* in particular which is involved in the metabolism of the majority of  $\beta$ -blocker medications (31).

## PHARMACOGENOMICS OF ACE INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS

Both ACE inhibitors and angiotensin II receptor blockers (ARB) work by antagonizing the renin-angiotensin-aldosterone system (RAAS) and are used for the treatment of hypertension in various cardiovascular conditions. ACE inhibitors prevent the conversion of angiotensin I into angiotensin II which is the main active enzyme of the RAAS system. ARBs block the stimulation of angiotensin II receptors (AGTR1 and AGTR2) by angiotensin II (34). As is the case with most other medications utilized in the treatment of CHD patients, there is a high variation in response to the prescribed medications.

The effectiveness of both of these classes of medications in the reduction of blood pressure has been established a long time ago, although only recently pharmacogenomic studies have been conducted to evaluate the possible effect of polymorphisms within the RAAS system genes. There have been many studies on polymorphisms such as an insertion / deletion (I / D) polymorphism in the *ACE* gene, a Met235Thr and Thr207Met polymorphisms in the angiotensinogen (*AGT*) gene and some research with a poly-

morphism in the gene encoding AGTR1 (31, 35). Currently, the majority of these studies are focusing on insertion / deletion (I / D) polymorphisms in the *ACE* gene which codes one of the key enzymes in the RAAS (9).

Despite, or perhaps because of, the amount of research on the *ACE* gene polymorphisms, a lot of conflicting results on the CHD and other cardiovascular disease development and progression have been reported (31, 36). A six-year hazard rate showed no significant differences in CHD, stroke or mortality among patients with different *ACE* genotypes treated with ACE inhibitors or ARBs (31, 37). Overall, there have been a wide variety of studies showing inconclusive results with the I / D polymorphism in the *ACE* gene; therefore, currently there is no definitive association between this *ACE* polymorphism and response to either ACE inhibitor or ARB treatment.

Angiotensinogen (*AGT*) Met235Thr polymorphism has also received a lot of attention (34). *AGT*, which is a precursor to angiotensin II, is supposed to influence the mechanism of action of ACE inhibitors (31). Studies have shown that people with 235Thr alleles have higher circulating levels of angiotensin in their blood plasma as compared with the 235Met allele carriers. The same studies have indicated a possible association between the 235Thr allele and increased blood pressure (31). These findings have naturally led to investigations of whether the alleles of the mentioned polymorphism affect the patient's response to ACE inhibitors, although no conclusive evidence has been found (31, 34).

*AGTR1* is another candidate gene in which the A1166C polymorphism may be important for the effect of ARBs. However, no unambiguous conclusions can be drawn from the published results; therefore, based on the currently available data, it is possible to say that polymorphisms in the *ACE*, *AGT* or *AGTR1* genes do not affect blood pressure when patients are treated with ACE inhibitors or ARBs (31, 34, 37).

## PHARMACOGENOMICS OF DIURETICS

Diuretics, although rarely used as monotherapy, are very important in the treatment of hypertension. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the majority of the compelling indications requiring hypertensive treatment(s) have thiazide diuretics listed as a first-line choice (36). It should be noted that this group of medications, similarly as many others used for the treatment of cardiovascular diseases or related conditions, have a severe inter-patient response variability (38). There have been several pharmacogenetic studies regarding the adducin gene, which is a cytoskeletal protein consisting mainly of an  $\alpha$  and  $\beta$  subunit encoded by *ADD1*, *ADD2*, and *ADD3* genes (38, 39). There has also been some research

into the atrial natriuretic precursor A (*NPPA*) gene and its contribution to inter-patient variability of response to diuretics (40).

The  $\alpha$ -adducin gene (*ADD1*) is the best studied adducin gene because of its well-known association with thiazide diuretics.  $\alpha$ -Adducin has a function in renal tubular sodium reabsorption by sodium / potassium ATPase (23). The Gly460Trp polymorphism in *ADD1* has been associated with a form of salt-sensitive hypertension (8). The association of a greater reduction in blood pressure when treated with hydrochlorothiazide with 460Trp allele compared to the 460Gly (wild type) allele was demonstrated in several studies (9, 37). The 460Trp variant carriers treated with a thiazide diuretic had a significantly lower risk of both MI and stroke. However, diuretic therapy with the wild type allele was not associated with the risk of MI and stroke (39). Not all studies on the association of *ADD1* gene polymorphisms with the lowering of blood pressure and CHD risk when treated with antidiuretics (and chlorthalidone in particular) were in concordance as some of them failed to find any association (9).

The *NPPA* gene codes a large precursor peptide (containing a signal peptide) which is processed to release cardiotensin from the N-terminus and the atrial natriuretic peptide (ANP) from the C-terminus with natriuretic-diuretic activity by controlling electrolyte homeostasis and extracellular fluid volume (40). The *NPPA* T2238C polymorphism has been the main focus of recent studies concerning the pharmacogenomics of diuretic drugs. The C allele carriers of the *NPPA* T2238C polymorphism were associated with lower CHD event rates as well as larger reductions in blood pressure compared to the T allele carriers when treated with chlorthalidone as compared with patients treated with calcium channel blocker amlodipine. The TT genotype was associated with a greater risk of MI, stroke and all-cause mortality when treated with chlorthalidone as compared with amlodipine (40).

The above-mentioned and some other studies have shown reliable positive results making pharmacogenetic testing a viable solution for the adjustment of dosage of diuretic drugs which would be a useful tool in the management of cardiovascular diseases in the future (38, 40).

## CONCLUSIONS AND THE FUTURE OF PHARMACOGENOMICS

The rapid progress achieved in genomic medicine, especially after completing the Human Genome Project, has helped propel the strive of medicine towards the goal of individualized drug therapy. Pharmacogenetics has evolved into pharmacogenomics, with a progress of genome-wide techniques to study the role of inheritance in drug response phenotypes. These developments will eventually make it

possible for physicians to more accurately predict individual variations in drug response. Implementation of the Genetic Information Nondiscrimination Act of 2008 in the US and similar legislation in the European Union will help to address patients' concerns with regard to the use of this type of clinical genetic information (41).

Pharmacogenomics, and cardiovascular pharmacogenomics in particular, can prove to be cost-effective by hopefully decreasing the number of patients who experience adverse reactions or use the drugs that provide little or no therapeutic effect. Researchers have been conducting pharmacogenomic studies on a variety of topics within cardiovascular medicine for years. With a few important exceptions, the pharmacogenomic research in cardiovascular medicine has provided conflicting results, thus delaying the implementation of genetic testing to create genotype-based medication dosing algorithms.

As we have seen with warfarin and to some extent with clopidogrel, the practical use of pharmacogenomics in the future is plausible. Currently there are genetic screening tests for CYP2C9 and VKORC1, which could affect warfarin-dosing protocols, are in progress. Changes were also made within warfarin package insert to include this information, and the United States Food and Drug Administration "highlights the opportunity for health care providers to use genetic tests to improve their initial estimate of what is a reasonable warfarin dose for individual patients" (42). Therefore, hope remains that individualized CHD treatment and prevention are just round the corner and will be in full swing in the upcoming 10 years.

Received 12 April 2011

Accepted 26 May 2011

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#### FARMAKOGENOMIKA: INDIVIDUALIZUOTOS MEDICINOS PERSPEKTYVA GYDANT KORONARINĘ ŠIRDIES LIGĄ

##### Santrauka

Nors šiuo metu medicinos praktikoje jau egzistuoja vaistų dozavimo algoritmai, tačiau neretai gydytojai tinkamiausią vaisto dozę konkrečiam pacientui, kuri teiktų jam didžiausią terapinę naudą, nustato bandymų būdu. Šiuo metu vis daugėja įrodymų, kad skirtingam organizmo atsakui į gydymą tam tikrais vaistais iš dalies, o kartais ir iš esmės turi įtakos paciento genominės sandaros ypatumai. Nepaisant spartaus farmakogenomikos mokslo progreso, šandien yra nedaug priemonių, padedančių efektyviai spręsti individualizuoto vaistų dozavimo problemas.

Šios apžvalgos tikslas yra įvertinti variaciją genuose, kurie turi įtakos vaistų, naudojamų gydant koronarinę širdies ligą (KŠL), veikimui. Tarp vaistų, naudojamų KŠL gydymui, yra antikoagulantų, beta adrenoreceptorių blokatorių, diuretikų, statinų, antiaritmikų, angiotenziną konvertuojančio fermento inhibitorių, angiotenzino II receptorių blokatorių grupėms priklausančių vaistų. KŠL farmakogenomikos tyrimai šiuo metu yra tarp kertinių kardiologijos mokslo plėtros sričių, o daugybe šiuo metu vykdomų tyrimų vis dažniau yra nustatomi reikšmingi rezultatai, leidžiantys manyti, jog artimiausiu metu farmakogenetika taps neatsiejama individualizuotos medicinos dalimi.

Daugelio pastarojo meto farmakogenominių tyrimų rezultatai yra prieštaringi, tačiau tokių vaistų, kaip varfarinas ar klopidogrelis, veikimą lemiančių genų tyrimų rezultatai leidžia manyti, jog netolimoje ateityje galime tikėtis praktinio farmakogenominių tyrimų panaudojimo individualizuotoje medicinoje.

**Raktažodžiai:** farmakogenomika, koronarinė širdies liga, vaistai