

## Role of Pharmacogenetics on Response to Statins: A Genotype-based Approach to Statin Therapy Outcome

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### ABSTRACT

Statins are widely prescribed and very effective drugs in prevention of cardiovascular disease. There is large variability between individuals in drug response to statins. It is demonstrated that genetic variation influences the inter-individual differences in both pharmacokinetic and pharmacodynamic pathways, which leads to altered efficacy and enhanced adverse drug reactions.

Pharmacogenetics aims to provide maximum clinical efficacy together with minimized adverse drug reactions and possibly letting “personalized medication” possible. Several pharmacogenetic gene studies including single nucleotide polymorphisms have been performed related to candidate genes that may impact the enzymes, metabolisms, transport systems and hence may alter pharmacokinetic and pharmacodynamic properties of statins.

This article reviews, the polymorphic genes CYP3A4, CYP3A5, CYP2D6 and CYP2C9 that are members of the cytochrome P450 (CYP) enzymatic pathways in respect to their effect on altering of statin metabolism. In addition, the effects of HMG-CoA reductase and apolipoprotein E genes and their variants on lipid lowering efficacy of statins are evaluated. Variants of the other genes associated with the clinical events after statin therapy including SLCO1B1, CETP, ABCB1, ABCB2 (BRCP), KIF6 and other genes are also discussed.

Since genetic markers are predictive of response to statin therapy, research in the field of pharmacogenetics aims to guide personalized treatment of hypercholesterolemia. With this purpose their potential application in clinical practice should be investigated in large cohorts of patients and especially genome-wide association

studies. Further trials will determine whether any pharmacogenetic testing would be beneficial in providing a “tailoring treatment” of statins in the management of cardiovascular disease.

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**Key words:** Cardiovascular disease; Lipid lowering; Pharmacogenetics; Polymorphism; Statins; Statin myopathy

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### INTRODUCTION

Coronary heart disease (CHD) continues to be the leading cause of morbidity and mortality among adults in Europe and North America<sup>[1,2]</sup>. Hypercholesterolemia is known to be a highly significant risk factor in the development of cardiovascular disease (CVD)<sup>[3]</sup>. Statins are a wide group of drugs which blocks cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Prescription and clinical use of statins has reached excessive numbers and they became the most prescribed class of drug worldwide since their introduction into the marketplace in 1986<sup>[4]</sup>. Despite their proven efficacy on lipid lowering and reducing the risk of cardiovascular events and protection against CVD, there is considerable inter-individual variability to statins in terms of both efficacy and toxicity<sup>[5,6]</sup>.

Pharmacogenetics refers to genetic differences in metabolic pathways and investigates the role of genetics in determining an individual's response to a drug. Over the past decade studies have focused on the issue of which genetic factors contribute to this variation in therapeutic and adverse effects of statins<sup>[7,8]</sup>. Despite their wide use only one-third of patients treated with statins reach their targeted plasma low density lipoprotein-cholesterol (LDL-C) levels<sup>[9]</sup>; in addition pharmacogenetic variability may also lead to serious adverse drug reactions (ADR) including statin associated myopathy which can range from mild myalgia to severe muscle myopathy<sup>[10]</sup>.

Recent pharmacogenetic studies revealed functional polymorphisms including single-nucleotide polymorphisms (SNP's)

that result in an amino-acid change or other variation in genes encoding several drug transporters or drug metabolizing enzymes which may also alter these effects of statins besides other individual environmental factors<sup>[3,5,11,12]</sup>. This paper summarizes the current knowledge of the role of pharmacogenetic factors in efficacy and ADR's of statins which are in clinical use.

## GENETIC FACTORS ASSOCIATED WITH PHARMACOKINETIC PATHWAYS OF STATINS

### Cytochrome P450 Enzymes (CYP Enzymes)

Statins are highly extracted and mostly metabolized in the liver by the microsomal cytochrome P450 (CYP) system that converts these lipophilic drugs into hydrophilic molecules. Statins, such as lovastatin, atorvastatin and simvastatin are mainly metabolized by CYP450 isoenzyme CYP3A4 and fluvastatin by CYP2C9, conversely pravastatin and rosuvastatin, which are hydrophilic molecules undergo minimal CYP-mediated metabolism<sup>[13-16]</sup>. Beside CYP3A4 and CYP2C9, CYP2D6 and CYP3A5 contribute to the metabolism of certain statins. Since CYP450 enzymatic pathways are considerably involved in biotransformation of statins, polymorphisms affecting these enzymes may impact the statin metabolism and drug efficacy<sup>[17-20]</sup>.

It was demonstrated that in patients treated with 10 mg/day of atorvastatin, the A-290G variant in the CYP3A4 promoter caused a reduced response and hence an smaller decrease in LDL-C level, whereas the M445T variant carriers showed an enhanced efficacy response and lower LDL-C levels compared with the wild type allele (non carriers)<sup>[21]</sup>. In addition, it was reported that the \*4<sup>[18]</sup> and \*1 G alleles<sup>[19]</sup> of CYP3A4 were associated with enhanced response to related statins.

Carriers of the CYP3A5\*1 allele are referred to as expressers of CYP3A5, whereas CYP3A5\*3 allele (rs776746) reduces expression of CYP3A5 and is associated with difference on efficacy of certain statins<sup>[22-24]</sup>. Kivisto *et al* reported an association between the CYP3A5 genotype and lipid response to lovastatin, simvastatin and atorvastatin and found higher LDL-C reduction in carriers of the CYP3A5\*3 allele compared to CYP3A5 expressers<sup>[25]</sup>. Contrary to this finding, there are some other trials which either did not report any association between the CYP3A5 polymorphism and lipid lowering response<sup>[26]</sup> or demonstrated contradictory results<sup>[24]</sup>. Although there is not sufficient data to support a major involvement of CYP3A5 enzymatic pathway in statin metabolism, results from studies mentioned above suggest that CYP3A5 genotype differences could affect the efficacy of treatment with certain statins<sup>[27]</sup>.

Carriers of the CYP2D6 homozygous mutant alleles (CYP2D6 mut/mut), which are defined as poor metabolizers (PM) add to at least 10% of the general population, and ultra-rapid metabolizers (UM) of this gene also have similar high percentage<sup>[14,27]</sup>. A study investigating CYP2D6 variants revealed that PM demonstrate increased lowering of total cholesterol (TC) and higher incidence of side effects due to the decreased metabolism of simvastatin and hence result in increased plasma concentrations of the drug compared with the wild-type (CYP2D6 wt/wt) carriers<sup>[28]</sup>. Similar results observed in another study replicated that carriers with low activity variants display higher efficacy of statin treatment<sup>[29]</sup>. As CYP2D6 is not mainly involved in statin metabolism, how it plays a role in statin treatment efficacy is still unclear<sup>[14]</sup>.

It is suggested that CYP2C9 may be involved partially in the metabolism of rosuvastatin, although rosuvastatin undergoes minimal

CYP-mediated metabolism (like pravastatin and pitavastatin). Potential drug interactions should be taken into consideration since CYP2C9 activity is inhibited by some drugs and therefore statin levels and efficacy could be affected<sup>[30,31]</sup>. As yet evidence regarding polymorphisms within CYP genes which alter the metabolism and efficacy of statins is insufficient, more data from further investigations related to these interactions would be beneficial for the prediction of effectiveness and toxicity.

### Statins and Cellular Transporters

There are important energy and non-energy-mediated cellular transport systems involved in drug transportation. Influx and efflux transporters expressed on the plasma membranes considerably modify the absorption, distribution and elimination and consequently the efficacy and toxicity of statins<sup>[32]</sup>. ATP (adenosine triphosphate)-binding cassette (ABC) and solute carriers (SLCs) are of the most significant super-families of these membrane transporters<sup>[13,33,34]</sup>.

### ATP-Binding Cassette Transporters (ABC Transporters)

One of the transport systems, the ATP-binding cassette subfamily B (ABCB), is responsible for the liver drug efflux, and influences the lipid-lowering activity of statins. Several genes associated with the ABC transporters family are involved in both pharmacokinetic (ABCB1, ABCB2, ABCG2 and ABCB11) and pharmacodynamic (ABCA1, ABCG5 and ABCG8) properties of statins<sup>[35]</sup>.

The effects of ABCB1 transporter variants (which encodes P-glycoprotein, an efflux transporter), on the variability in pharmacokinetics of statins have been reported in several studies<sup>[33,36]</sup>. The c.1236C>T, c.2677G>T and c.3435C>T polymorphisms within the ABCB1 gene, and CGC and TTT haplotypes are the most commonly investigated variants<sup>[37]</sup>. ABCB1 3435T allele leads to impairment of efflux function and could enhance intestinal absorption of statins<sup>[17]</sup>. It has been found that carriers of the TTT genotypes express low function and have higher area under curve (AUC) values of simvastatin acid and atorvastatin compared with the common CGC haplotype<sup>[38]</sup>. Another study revealed that carriers of the ABCB1 1236T variant allele had a greater reduction in TC and LDL-C with simvastatin treatment compared with the homozygotes with the wild type allele and similar results were observed for the 2677G>A/T polymorphism<sup>[26]</sup>. Peters *et al*<sup>[36]</sup> evaluated data from the Pharmaco-Morbidity Record linkage system of the Netherlands (PHARMO) study involving 668 cases with myocardial infarction and 1217 controls all treated with statins. They tested common variants of 24 tagging SNP's and found a significant interaction between statin therapy (simvastatin, atorvastatin, and pravastatin) and two SNP's within ABCB1 (rs3789244 and rs1922242).

The ABC transporters G5 (ABCG5) and G8 (ABCG8) are involved in intracellular cholesterol transport and mediate biliary excretion of cholesterol, thus impairment of this pathway could interact with cholesterol biosynthesis and response to statin treatment<sup>[39,40]</sup>. Kajinami *et al*<sup>[41]</sup> genotyped a group of patients treated with 10 mg of atorvastatin, and found that D19H variant allele (rs 11887534 SNP) in the ABCG8 was significantly associated with a greater reduction in LDL-C levels compared to the wild type homozygotes.

Another determinant of statin pharmacokinetics is the ABCG2 efflux transporter also known as breast cancer resistant protein (BRCP) (encoded in the ABCG2 gene), which modulates the absorption and elimination of statins including rosuvastatin and atorvastatin<sup>[42-44]</sup>. ABCG2 c.421C>A SNP results in a reduced BRCP transport activity, which has an important role in limiting the absorption of statins<sup>[39]</sup>. Variants of the ABCG2 efflux transporter (BRCP) were

evaluated by Keskitalo *et al* in two studies. Carriers of the c.421AA polymorphisms in ABCG2 gene were associated with 144% increases in the AUC of rosuvastatin and 72% for atorvastatin compared with the c.421CC genotype<sup>[45]</sup>, and similarly 111% increase for simvastatin lactone due to the decrease in the intestinal efflux of statins<sup>[46]</sup>.

### Organic anion transporting polypeptides (OATP's/SLCO Transporters)

Organic anion transporting polypeptides (OATP's) or solute carrier organic anion transporters (SLCO's) play a crucial role in drug uptake and efficacy as many other endogen organic compounds and are expressed in the liver, intestine and brain<sup>[32,47,48]</sup>.

Organic anion transporting polypeptide 1B1 (OATP1B1) previously known as OATP2, OATP-C and liver specific transporter 1, is a member of solute carrier OATP family coded by the SLCO1B1 gene. Under current nomenclature, the gene is referred to as SLCO1B1 and the protein as OATP1B1<sup>[49,50]</sup>. OATP1B1 is a 691-amino acid glycoprotein and it is one of the main influx transporters expressed on the plasma membrane of the hepatocytes in the liver<sup>[48,51,52]</sup>. Besides OATP1B1, there are some other OATP's; OATP1B3 is expressed exclusively in the liver, OATP1A2 in the liver, intestine and brain and OATP2B1 is localized and expressed in the liver, small intestine and skeletal muscle<sup>[39,53,54]</sup>. OATP1B1 is involved in transporting a number of endogenous and exogenous substances, including several bile acids, bilirubin, thyroid hormones, methotrexate<sup>[49,55]</sup> and statins. It has also been shown that all statins in clinical use are substrates of OATP1B1<sup>[56-60]</sup>. Many sequence variants have been found within the SLCO1B1 gene, located on chromosome 12<sup>[32,50]</sup>.

The c.388A>G and c.521T>C SNP's are the most frequently investigated polymorphisms and four types of haplotype are described related to presence of these polymorphisms, alone or in combination with each other in three haplotypes; SLCO1B1\*1b, \*5 and \*15 (reference haplotype is SLCO1B1\*1a)<sup>[32,44,50]</sup>. Haplotypes of SLCO1B1 and their transport activity from *in vitro* and *in vivo* studies are sited in table 1.

Several studies have investigated the effect of genetic polymorphisms including the SLCO1B1 gene and the two main variants c.388A>G and c.521T>C SNP's, which involve transport activity and affect statin transport<sup>[61,62]</sup>.

In a series of studies, the effects of the SCLO1B1 c.521T>C SNP, on the pharmacokinetics of fluvastatin, pravastatin, simvastatin, atorvastatin and rosuvastatin were investigated in the same 32 healthy young subjects<sup>[63-65]</sup>. In Pasanen *et al* study, both heterozygotes (TC) and homozygotes (CC) carriers of the c.521T>C polymorphism show increased plasma concentration of atorvastatin due to the decreased uptake into the liver<sup>[65]</sup>. When patients homozygous for the c.521CC were compared with patients expressing the c.521TT allele, based on the AUC analysis, the largest effect was 221% increase in exposure to simvastatin acid (active form) in homozygous patients<sup>[64]</sup>. Further

AUC analyses from other studies reported a 173% increase in AUC values for pitavastatin, 144% for atorvastatin, 90% for pravastatin and 87% for rosuvastatin<sup>[60,66,67]</sup>. These differences may be due to different pharmacokinetic properties of the statins and other influx transporters which involve their uptake<sup>[32]</sup>. The individual combination of haplotypes affects transporter function. While c.388A>G haplotype leads to an enhanced OATP1B1 activity and decreases the statin concentrations<sup>[61]</sup>, the c.521T>C SNP increases statin levels by impairing this activity<sup>[66]</sup> (Table 1).

Despite some *in vitro* studies which show that OATP1B1 is likely to have a similar transport activity to the reference haplotype 1\*a<sup>[56,62,68]</sup>, some small *in vivo* studies with pravastatin suggest that \*1b allele leads to an increased transport activity compared with \*1a allele<sup>[61,69]</sup> (Table 1). Further studies with other statins are required to determine more information about the effect of the \*1b allele. Studies show that the presence of a single copy of the \*15 allele is associated with a significant decrease in hepatic uptake, and this increase in plasma AUC is enhanced when two copies of this haplotype are present<sup>[63,65,70]</sup>. According to the results of *in vivo* pharmacokinetic studies a single copy of the \*15 allele leads to an increase in plasma AUC. This possible substrate specific effect is more notable when two copies of the \*15 allele are present. Consequently, many researchers have suggested that the presence of one or two variant alleles \*5 or \*15 haplotypes would lead to an attenuated lipid lowering response to related statins<sup>[50]</sup> (Table 1).

### OATP and Adverse Drug Reactions

It is suggested that adverse drug reactions including myopathy are related to the increase in plasma concentration of statins<sup>[64]</sup>. Since statin-induced myopathy is a concentration-dependent adverse drug reaction, researchers argue that when statins are especially used in high daily doses, the SLCO1B1 c.521>C SNP increases the risk of myopathy<sup>[32]</sup>. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine trial (SEARCH) Collaborative Group confirmed this risk for simvastatin, in a genome wide association study<sup>[71]</sup>. The study recruited 12,064 patients which were allocated to receive either 20 mg or 80 mg of simvastatin. After a follow up of 6 years, myopathy was identified in 85 patients of the high simvastatin (80 mg) group. When the 85 patients with myopathy were compared to a control group of 90 patients it was shown that a non-coding SNP in the SLCO1B1 gene (rs4363657) which is in strong linkage disequilibrium with the c.521T>C SNP ( $r^2=0.97$ ) was strongly associated with simvastatin induced myopathy. The odds ratio was 4.5 per copy of the c.521C allele, and this risk further increased among homozygous CC individuals (odds ratio 16.9). In the heart protection study, the association between c.521C and myopathy was replicated in a cohort of 16640 patients (with 23 confirmed cases of myopathy) on 40 mg/day simvastatin ( $p=0.004$ ); the relative risk of myopathy per C allele was 2.6<sup>[71]</sup>. The other study with the GWAS approach was the STRENGTH (Statin Response Examined by Genetic Haplotype Markers). In the mentioned study, 509 patients were randomized to receive low or high dose simvastatin, pravastatin or atorvastatin<sup>[72]</sup>. The SLCO1B1 5 genotype (c.521T>C SNP) was significantly associated with a gene-dose effect with any of adverse effects including discontinuing the trial for myalgia with or without reported increase in creatine kinase (CK)<sup>[72]</sup>. The study also revealed that an increased statin induced muscular toxicity is observed in female sex possibly associated with lower average body mass index (BMI) of women. Another important issue observed in the mentioned study is that polymorphism in SLCO1B1 and myopathy during therapy in other statins except simvastatin remains uncertain. Adverse effects to

**Table 1** Haplotypes of SLCO1B1 and in vitro and in vivo transport activity changes including the reference haplotype.

Haplotype	Nucleotide change	<i>In vitro</i> transport activity	<i>In vivo</i> transport activity
*1a	Wild type	—	—
*1b	c.388A>G	—	—↑**
*5	c.521T>C	↓*	↓
*15	c.388A>G c.521T>C	↓*	↓

Data from<sup>[32,39,44,50,56,61,62,66,68,69]</sup>.

↓: decreased activity; —: no change in activity; ↑: increased activity; \*except for simvastatin; \*\*Possibly substrate specific.

statins including discontinuation were reported by Donnelly *et al*<sup>[73]</sup> in over 4,000 type 2 diabetic patients treated with statins. Among these patients carriers of the SLCO1B1 5 variants had 2- fold increase in statin intolerance. All these results strongly indicate that the c.521T>C SNP may be a highly predictive marker for the attenuated response to lipid lowering effects of statins, especially simvastatin, including statin-induced myopathy.

## GENETIC FACTORS ASSOCIATED WITH THE PHARMACODYNAMIC PATHWAY OF STATINS

### Apolipoprotein E

Apolipoprotein E (ApoE) has multiple roles in lipid metabolism. It mediates lipid metabolism by binding to lipids and lipoprotein receptors and modulates the transport of very low-density lipoproteins (VLDL) and chylomicrons from plasma to the liver<sup>[74]</sup>. ApoE is a ligand for the LDL receptor, plays a significant role in cholesterol transport throughout the body, in addition affects intestinal absorption<sup>[17]</sup>. Apo E is a genetically polymorphic gene with three common alleles E2, E3 (wild type) and E4 alleles encoding proteins with increasing affinity for the LDL receptor respectively<sup>[75]</sup>. Since cholesterol clearance from the circulation is faster in E4 allele carriers than E2 and E3 allele carriers, downregulation of HMG-CoA reductase and low-density- lipoprotein receptor (LDLR) results in an increase in the plasma LDL-C concentrations. On the other hand, impairment of the clearance leads to upregulation of the synthesis of HMG-CoA reductase and hence lower LDL-C and LDLR in E2 carriers<sup>[17,75]</sup>. As a result, patients with the E2 genotype could benefit more from statin therapy and demonstrate greater cholesterol reductions compared with the E4 genotype<sup>[76-78]</sup>, but the literature is inconsistent. The GoDARTS (Genetics of Diabetes Audit and Research in Tayside) study revealed that one-third of patients of E4 variant could not reach expected target levels of LDL-C with statin treatment compared with patients possessing the E2 variant who reached the target LDL-C levels<sup>[78]</sup>.

There are many similar studies which report that the E4 allele is associated with a decreased response to statins compared with the E2 allele. A reduced therapeutic compliance with statin therapy (2-3 fold) was observed in E4 carriers, possibly explained by the lower therapeutic efficacy or adverse effects due to statins<sup>[79,80]</sup>. One study revealed that males with the E2 allele showed larger reduction of LDL-C and TC compared with females although baseline lipid levels were similar in both groups<sup>[77]</sup>. As a result it was suggested that the alterations in lipid-lowering effect of ApoE variants could be gender-specific. However, in a sub-study of the Scandinavian Simvastatin Survival Study (4S trial), although E4 carriers demonstrated reduced LDL-C lowering response, they benefited most from statin treatment with respect to reduction in mortality risk. The higher reduction in mortality risk is probably associated with the initial greater mortality risk of Apo E4 allele carriers compared with non-carriers<sup>[81]</sup>. The paradoxically enhanced benefit of statins in E4 carriers may also be explained by the “pleiotropic” anti-inflammatory effect of statins<sup>[75,82]</sup>. Nevertheless, in Regression Growth Evaluation Statin Study (REGRESS) data from 815 men with CHD who received either pravastatin or placebo could not confirm any association between ApoE genotype variation and statin treatment in terms of cardiovascular end points<sup>[83]</sup>. Similarly analyses from almost 8,000 patients from the Rotterdam study showed protective cardiovascular effects of statins were not

dependent on ApoE polymorphism<sup>[84]</sup>.

### Cholesteryl Ester Transfer Protein

The cholesteryl ester transfer protein (CETP) enzyme participates in the cholesterol transport from peripheral tissues back to the liver<sup>[74]</sup> and is also involved in the transport of triglycerides from LDL and very LDL (VLDL) to high-density lipoprotein (HDL )<sup>[27,85]</sup>. A common polymorphism in the CETP gene is Taq 1B variant and is associated with variations in lipid transfer function and hence elevated CETP and lower HDL-C levels<sup>[86,87]</sup>. Lower HDL concentrations are observed in patients with the B1B1 genotype of the CETP gene, besides increased risk of CHD compared with B2B2 genotype<sup>[88,89]</sup>. It was also observed that progression of coronary artery atherosclerosis was slower during pravastatin therapy in B1B1 carriers, whereas B2B2 carriers did not benefit sufficiently despite higher HDL levels<sup>[89]</sup>. In another study, diabetic patients treated with atorvastatin were evaluated and despite B1B1/CC polymorphism carriers initially showed more atherogenic lipid profile, they had higher HDL-C levels as a better response compared with carriers of the B1B2 and B2B2 variants<sup>[90]</sup>.

In the West of Scotland Coronary Prevention Study (WOSCOPS) the B2B2 genotype had elevated HDL-C levels at baseline. Although associated with only 0.5% increase in plasma HDL-C levels, B2B2 genotype was found to have a 30% decreased risk of cardiovascular end-points than those of B1B1 homozygotes<sup>[91]</sup>. In Regression Growth Evaluation Statin Study (REGRESS) cohort, 10-year follow-up analysis reported similar results. Despite inadequate HDL-C levels, lower risks in myocardial infarction (MI) and death from ischemic heart diseases were observed with statin therapy for B1B1 carriers compared to B2 carriers<sup>[92]</sup>. Recently, another large meta-analysis including nearly 13,000 patients revealed a significant association between the Taq1B genotype and HDL-C levels but did not find any association between altered efficacy in statin therapy and the Taq1B polymorphism<sup>[93]</sup>. Many other studies also investigated the CETP polymorphism, and reported contradictory results regarding Taq1B polymorphism and its effect on efficacy of statin treatment or on cardiovascular events in patients with CHD treated with statins<sup>[94-96]</sup>.

### HMG-CoA Reductase Enzyme

Statins are competitive inhibitors of HMG-CoA reductase (HMGCR), encoded by the HMGCR gene, is the rate limiting enzyme for the biosynthesis of cholesterol and converts HMG-CoA to mevalonic acid<sup>[97]</sup>. Variants of the HMGCR gene include SNP12 (rs17244841) and SNP 29 (rs17238540), both which are observed in equal frequencies and tightly linked to each other. These SNP's alter the response to statin therapy and lead to less reduction of TC and LDL-C levels during statin treatment<sup>[98]</sup>. The PRINCE study (Pravastatin Inflammation/ C reactive protein Evaluation) investigated 148 SNP's in ten candidate genes involved in lipid metabolism in 1536 participants. The researchers reported that SNP 12 and SNP 29 were significantly associated with a reduced response to pravastatin therapy; 22% less in TC and 19% less in LDL-C levels compared with participants who did not bear either of this alleles<sup>[98]</sup>. The GoDARTS study showed that 51% of G allele carriers and 28% of T allele carriers displayed a failure to achieve treatment targets<sup>[99]</sup>.

However, the data from the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) trial<sup>[100]</sup> could not indicate any relationship between these SNP's and lipid responses and clinical outcomes. More data from new studies are needed to show whether there is an influence of HMGCR gene on the lipid response variability of statin treatment.

### KIF6 Gene

The kinesin-like protein 6 is encoded by KIF6 gene and participates in intracellular molecule transport in several tissues, including the vascular system<sup>[17,101]</sup>. Findings of several studies confirmed that the Trp719 Arg (rs20455) SNP in the KIF6 gene could alter the responses to statin treatment<sup>[102-104]</sup> and is associated with CHD<sup>[103-107]</sup>. The analysis of the Comparison of Intensive and Moderate Lipid Lowering with Statins after Acute Coronary Syndromes (PROVE IT-TIMI 22) study has shown an increased reduction regarding the risk in cardiovascular end points by statin therapy<sup>[102]</sup> in carriers of the KIF6 Trp719 Arg allele compared with non-carriers. Two other clinical trials, Cholesterol And Recurrent Events (CARE) trial and West Of Scotland Coronary Prevention Study (WOSCOPS)<sup>[103]</sup> revealed similar results and confirmed that carriers of this SNP obtain significantly increased benefit from statin therapy than that of non-carriers. Nevertheless, since some other trials reported inconsistent results<sup>[101,108]</sup>, the association between the KIF6 polymorphism and cardiovascular events and effects on response to statins has not been exactly proven.

### Other polymorphic genes

Genetic variation in LDL-C related candidate genes have been investigated by researchers in some studies. Some alternations in the LDL-receptor gene (LDLR gene), encoding the LDL receptor, result in familial hypercholesterolemia<sup>[17,109]</sup>. Expression of LDL receptors is indirectly up-regulated due to inhibition of HMG-CoA reductase enzyme during statin treatment<sup>[27,110]</sup>. Mutations in LDLR gene could lead to alterations in lipid metabolism and expression of LDL receptors, thus altering lipid lowering response to statins<sup>[109,111]</sup>. However, it is difficult to interpret the inconsistent results from several studies because of the baseline lipid level differences due to the genetic variations<sup>[85]</sup>. Sterol regulatory element-binding protein 2 (SREBP-2) is a transcription factor, which is induced by statins, that activates the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene which regulates the number of membrane LDL receptors by degradation<sup>[27,112]</sup>. Genetic variations within PCSK9 gene were investigated and inconsistent results were obtained<sup>[113,114]</sup>. Depending on their type, variants of this gene could lead to enhanced or impaired functions on LDL-receptor expression, therefore a polymorphism in PCSK9 may alter the response to statin treatment since treatment success depends on upregulation of these receptors<sup>[110,112]</sup>. Observations in several studies propose that polymorphisms affecting this gene play an important role in LDL receptor expression and also affect the response to statins<sup>[110,115,116]</sup>.

Polymorphisms in genes, which modulate the vascular smooth muscle function, are suggested to play a significant role in the muscular side effects during statin therapy<sup>[14,117]</sup>. Researchers have also investigated the polymorphisms in other genes involved in the lipid-independent pleiotropic effects of statins, which alter the inflammation process of CHD, including eNOS, encoding the enzyme endothelial nitric oxide synthase (eNOS) and IL6 encoding interleukin 6 (IL-6)<sup>[17,113,114,118]</sup>. Evidence from *in vivo* and *in vitro* studies indicated that eNOS polymorphisms modulate the responses to statins<sup>[119-122]</sup>. eNOS -786 T >C polymorphism is the most studied variant and carriers of the C allele show decreased eNOS transcriptional activity up to 50% than those of non-carriers<sup>[123,124]</sup>. A clinical study investigating 786 T >C polymorphism concerning atorvastatin treatment in healthy volunteers, revealed that CC genotype showed increased nitric oxide (NO) availability and antioxidant effects compared to TT genotype<sup>[121]</sup>. Since carriers of the CC genotype are more susceptible to develop CVD, it is suggested

that statins could induce endogen NO formation and hence prevent enhanced cardiovascular risk<sup>[118]</sup>. However, the clinical evidence regarding the effectiveness and prophylactic use of statins in cases with specific genotypes (CC genotype for eNOS polymorphism) in order to lower cardiovascular events is not yet sufficient.

## SUMMARY

Statins are widely prescribed and highly effective drugs in cardiovascular drug treatment. Because there is large variability in clinical response with their lipid lowering efficacy and adverse drug reactions, several pharmacogenetic gene studies have been carried out and different results have been reported associated with genetic variations in response to statin therapy (Table 2). Since statins are mainly metabolized in the liver by the CYP enzymes, the relationship between polymorphisms affecting these enzymatic pathways and statin efficacy has been detected in some studies. CYP3A4 variants A-290 G and M445T<sup>[21]</sup> and also CYP3A5\* 3 allele<sup>[25]</sup> have been shown to alter the lipid lowering response to some statins and LDL-C levels. Low activity variants of CYP2D6 (PM) display decreased metabolism of certain statins and lead to lower LDL-C levels<sup>[28]</sup>. Important genes associated with the lipid lowering response to statin therapy include the HMGCR and APOE genes. There is a significant amount of evidence that variations in the HMGCR gene (SNP 12 and SNP 29) influence the lipid-lowering efficacy of statins and cause less reduction of LDL-C and TC levels<sup>[98]</sup>. The ApoE E2/E3/E4 polymorphism has been shown to alter the efficacy of statin treatment<sup>[78-80]</sup>. But the results are still not strong enough to know whether it impacts the course of CHD<sup>[81,83]</sup>. Some other important genes associated with the clinical events after statin therapy consist of SLCO1B1, CETP, ABCB1, ABCB2 (BRCP) and KIF6 genes<sup>[6]</sup>. Studies in drug transporter variants have shown that ABC and OATP transporting systems significantly are involved in the absorption and disposition of statins. SLCO1B1 c.388A>G and c.521T>C polymorphisms have been widely investigated and revealed that the c.521T>C SNP (\*5 or \*15 haplotypes) is related to reduced transporter activity and increases in AUC values of several statins<sup>[60,63,66,67]</sup>. There is also convincing evidence for association between the SLCO1B1 c.521C allele and increased risk of statin induced myopathy, particularly in patients on high dose of statins<sup>[63,70-72]</sup>. ABCB1 gene c.3435C >T and c.1236C>T polymorphisms have been shown to affect the response to statin treatment<sup>[38,125]</sup>. c.421C>A SNP in ABCG2(BRCP) gene has led to reduced BRCP transport activity and carriers of the c.421AA polymorphisms have increased AUC of statins than those of c.421CC genotype<sup>[45,46]</sup>. Some other studies show that the Taq1B variants of the CETP gene have been associated with decreased plasma HDL-C levels as well as variable benefit response to statin therapy<sup>[89,92]</sup>. Little is known about the contributions of other gene variants in statin response, and more clinical trials are required to assess their influence on statin therapy.

## CONCLUSIONS AND CLINICAL IMPLICATIONS

Over previous years a group of studies have identified polymorphisms in the pathways associated with the variation in statin response. High technology with respect to for detecting e.g. SNP's associated with differences in drug responses of increased adverse effects have lead to easier access to pharmacogenetic data. Although application of pharmacogenetic information to clinical practice in some fields has demonstrated benefit in quality adjusted life year assessments, there still isn't sufficient information or proof for clinicians to personalize

**Table 2** Effects of genetic variants associated with statin response and outcomes.

Gene	Mutation/variant	Effects	Results/Outcomes
CYP3A4	A-290G M445T	Alterations on statin metabolism and efficacy (atorvastatin)	-A-290G variant caused reduced response and higher LDL-C levels with statin. - M445T variant showed lower LDL-C levels <sup>[21]</sup>
CYP3A5	CYP3A5*3 allele	Reduced expression of CYP3A5 and alterations on efficacy of certain statins (lovastatin, simvastatin, atorvastatin)	-CYP3A5*3 allele caused higher LDL-C reduction with related statins compared with *1 expressers <sup>[25]</sup>
CYP2D6	CYP2D6 mut/mut	Alterations on statin metabolism and efficacy (simvastatin)	-PM with mut/mut allele demonstrated enhanced lowering of LDL-C and higher incidence of side effects than wild type (wt/wt) carriers <sup>[28]</sup>
SLCO1B1 (OATP'S)	521T>C	Reduced transport activity of statin (simvastatin, atorvastatin, rosuvastatin, pitavastatin, pravastatin) (simvastatin, pravastatin, atorvastatin)	-Associated with increased AUC levels of various statins <sup>[63,64,65,66]</sup> -Relative enhanced risk of statin-induced myopathy (simvastatin) <sup>[71,73]</sup> -Gene-dose related effect with any of adverse effects including myalgia (simvastatin) <sup>[72]</sup>
	*15 haplotype (521T>C and 388A>G)	Reduced transport activity of statin (Various statins)	- *15 haplotype leads to an increase in plasma AUC of statins <sup>[60,63,65]</sup>
ABCB1	3435C>T	Impaired efflux function (simvastatin, atorvastatin)	-TTT genotypes express low function and higher AUC values of statins compared with non carriers <sup>[38]</sup>
	1236C>T	Impaired efflux function (simvastatin)	-Carriers of 1236T variant had higher LDL-C reduction and 2677G>A/T variants showed similar results <sup>[26]</sup>
	2677G>A/T	Limited statin absorption (rosuvastatin, atorvastatin, simvastatin)	-421AA polymorphism showed increased AUC levels of statins than the 421CC genotype <sup>[45,46]</sup>
ABCG2	421C>A	-Altered HMG-CoA reductase levels -Altered lipid response to statins	-E4 allele had less reduction in LDL-C with statins whereas lower LDL levels in E2 carriers compared with non-carriers <sup>[76,78,79,80]</sup>
APOE	E2/E3/E4	-Associated with reduced cardiovascular events (Various statins) -Variations in lipid transfer function	-E4 carriers benefited more from statin treatment with respect to reduction in mortality risk <sup>[81]</sup>
CETP	Taq1B (B1B1, B1B2, B2B2 genotypes)	-Elevated CETP and lower HDL-C levels - Associated with reduced cardiovascular events (Various statins)	-B1B1 genotype associated with lower HDL-C and increased risk of CHD compared with B2B2 carriers <sup>[86,88,90]</sup> -Less progression of atherosclerosis with statin therapy in B1B1 genotype whereas B2B2 did not benefit sufficiently (increased 10-year CV events) <sup>[89,92]</sup>
HMG-CoA reductase	SNP 12 SNP 29	Reduced response to statin therapy (Various statins)	-Either SNP 12 or SNP 29 carriers had less reduction of TC and LDL-C levels during statin treatment than non carriers <sup>[98,99]</sup>

AUC: Area under curve; CHD: Coronary heart disease; CV: Cardiovascular; HDL-C: High density lipoprotein cholesterol; LDL: Low density lipoprotein; LDL-C: Low density lipoprotein cholesterol; PM: Poor metabolizer; SNP: Single Nucleotide Polymorphism; TC: Total cholesterol.

statin therapy. However it could be possible that the knowledge and evidence about the genes and pathways associated with statin response might lead to improvements in personalized dosing and hence improve the outcome of statin therapy in cardiovascular drug treatment. In the future, it seems that a systematic genetic definition for some SNP's would contribute to the efficacy and safety of the statin treatment. Genetic variations identified by these studies should be tested in large cohorts of patients to evaluate their benefit in clinical practice. Therefore multi-gene haplotype approaches especially GWA studies are needed to investigate which genetic pathways and genetic variations are involved in the alterations during statin therapy outcome.

In spite of the great number of published studies in pharmacogenomics of statin therapy there is no precise data to apply genetic testing for statins just yet and implementation in clinical practice is still far away.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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