

Clinical Implications of Pharmacogenetic Variation on the Effects of Statins

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Abstract

The last decade has seen an increase in the trend of HMG-CoA reductase inhibitor (statin) usage in the Western world, which does not come as a surprise noting that the latest American Heart Association heart and stroke statistics indicate an alarming prevalence of 80 million Americans (one in three) with one or more forms of diagnosed cardiovascular disease (CVD). Meta-analysis of several large-scale, randomized clinical trials has demonstrated statins to be efficacious in significantly reducing CVD-associated mortality in both primary and secondary prevention. Despite their proven efficacy, statins have also gained attention with respect to adverse drug reactions (ADRs) of muscle myopathy, derangements in hepatic function and even ADRs classified as psychiatric in nature. The depletion of cholesterol within the myocyte cell wall and/or the depletion of key intermediates within the cholesterol synthesis pathway are hypothesized as possible mechanisms of statin-associated ADRs. However, pharmacogenetic variability may also be a risk factor for ADRs and can include, for example, enzymes, transporters, cell membrane receptors,

intracellular receptors or components of ion channels that contribute to the pharmacokinetics or pharmacodynamics of response to a particular drug. The cytochrome P450 (CYP) enzymatic pathways that comprise the polymorphic genes, *CYP2D6*, *CYP3A4* and *CYP3A5*, and also a hepatic transporter, solute carrier organic anion transporter (*SLCO1B1*), which is a single nucleotide polymorphism discovered to be associated with statin-induced myopathy through a genome-wide association study, are discussed with respect to their effect on altering the pharmacokinetic profile of statin metabolism. Variants of the *Apolipoprotein E (APO-E)* gene, polymorphisms in the *cholesteryl ester transfer protein (CETP)* gene, the *HMG-CoA reductase* gene and other proteins are discussed with respect to altering the pharmacodynamic profile of statins. Pharmacogenetics and its application in medicine to individualize drug therapy has been previously shown to be clinically and economically beneficial through quality-adjusted life-year assessment. Therefore, polymorphisms affecting the pharmacokinetic and pharmacodynamic profiles of statins, which are widely used in therapy, with their potential application in the personalized prescribing of statin therapy, need further research. In this review, we update the recent literature with respect to genetic polymorphisms that may influence the pharmacokinetics and pharmacodynamics of statin therapy, and consider the relevance of these findings to the efficacy of treatment, prevention of ADRs and what this may mean for patient tolerance and compliance.

1. The Contribution of Genetic Variation to Differences in Statin Efficacy

In recent years it has become apparent that genetic variation contributes to interindividual differences in pharmacokinetics and pharmacodynamics (pharmacogenetics), and that this may impact on responses to therapeutic drugs. The focus of this review is on pharmacogenetic factors that may alter the response to HMG-CoA reductase inhibitors (statins), hence leading to altered efficacy of the drug, which may result in adverse drug reactions (ADRs). Compared with all lipid-lowering medicines, the percentage of statins dispensed in US pharmacies increased from 53.8% to 86.3% between 1991 and 1997.^[1] Consequently, between these years the dispensing of other cholesterol-lowering medication decreased.^[1] More recently, data from the US indicate that statin usage increased from 12.5 million users in 1999–2000 to 24 million in 2003–4.^[2] Furthermore, analysis of the Finland national prescriptions register shows an 11-fold increase in the number of statin prescriptions from 1995

(7.8 per 1000 inhabitants) to 2005 (88.9 per 1000 inhabitants).^[3] The increase in proportion of statins dispensed may be attributed to the superior efficacy of statin therapy compared with other drugs used in the management of dyslipidaemias. This superior efficacy has been demonstrated through several meta-analyses,^[4–7] in both the primary and secondary prevention of heart disease and attributable mortality. One such meta-analysis of 15 long-term clinical trials involving statin therapy revealed that there was a significant ($p < 0.0001$) reduction in the relative risk of a major coronary event by 33% in primary prevention and by 26% in secondary prevention trials.^[6] Similar meta-analyses have revealed comparable results with respect to the prevention of coronary heart disease (CHD) and cardiovascular disease (CVD) mortality.^[4,5,7] In 2005, atorvastatin and simvastatin were described as the first and second most prescribed medication worldwide, respectively^[8] and this trend is likely to continue, based on statins' clearly defined efficacy and significant reduction in the risk of CVD. More recently, an aggressive approach to lipid lowering has been recommended

for patients with existing coronary artery disease.^[9] A meta-analysis comparing the effect of either high- (80 mg/day) or low- (10–20 mg/day) dose statin therapy demonstrated the benefit of high-dose therapy.^[10] High-dose statin therapy, when compared with low-dose statin therapy across seven randomized clinical trials, on average produced a further reduction in low-density lipoprotein cholesterol (LDL-C) by 0.72 mmol/L (95% CI 0.60, 0.84). Intensive statin therapy also reduced the risk of myocardial infarction (MI) or coronary death (odds ratio [OR] 0.83; 95% CI 0.77, 0.91) and stroke (OR 0.82; 95% CI 0.71, 0.95).^[10]

However, statins have been associated with serious ADRs.^[11–14] The most commonly reported statin-associated ADRs include elevations in liver enzymes and myalgia, which is often associated with elevations in plasma creatine kinase (CK) levels. A meta-analysis of 18 randomized controlled trials revealed a total of 1017 ADRs in statin-treated patients compared with 811 in the placebo group, demonstrating that statin therapy significantly ($p < 0.008$) increased the risk of any adverse event by 39% compared with placebo treatment.^[14] More specifically, 316 incidents of myopathy were reported in the statin group compared with 253 in the placebo group ($p < 0.001$). Furthermore, there were 609 cases of abnormal liver function tests (i.e. transaminase levels $>3 \times$ the upper limit of normal [ULN]) in the statin group compared with 487 cases in the placebo group ($p = 0.002$).^[14] Another meta-analysis of 35 randomized clinical trials, including $>70\,000$ patients, revealed that the risk of myalgia (15.4% and 18.6% in the statin-treated and placebo groups, respectively) and rhabdomyolysis (0.2% and 0.1% in the statin-treated and placebo groups, respectively) with statin (simvastatin, atorvastatin, fluvastatin, rosuvastatin and lovastatin) therapy was not significantly elevated in the statin-treatment groups. The meta-analysis did, however, reveal a significantly raised risk ($p < 0.04$) of elevated transaminase levels in the statin-treated group (1.4% and 1.1% in the statin-treated and placebo groups, respectively).^[15] Myopathies and hepatotoxicity are classed as rare events and are reported to occur in 1–5% of all patients initiated on statin therapy.^[11,16]

ADRs as a whole can be a result of inter-individual risk factors such as drug interactions and the patient's age, liver and renal function, smoking and alcohol consumption.^[17] However, pharmacogenetic variability may also be a risk factor for ADRs and can include, for example, enzymes, transporters, cell membrane receptors, intracellular receptors or components of ion channels, which contribute to the pharmacokinetics or pharmacodynamics of response to a particular drug. Possibly, genes coding for proteins associated with the direct development of the disease or specific phenotypes may also contribute. The simplest cause of interindividual genetic variation in drug response is a point mutation of an allele, i.e. a single nucleotide polymorphism (SNP), which may impact on the protein-coding capacity of a gene, the way it is spliced or the way it is expressed or regulated. However, more recently, researchers have become aware of a wide range of structural variation in the human genome, including copy number polymorphisms, but the full relevance of these sources of variation for pharmacogenetic effects is yet to be appreciated.

Several articles have addressed the influence of pharmacogenetic variation on the efficacy and tolerance of statin therapy.^[18–25] In this review, we update the recent literature with respect to genetic polymorphisms that may influence the pharmacokinetics and pharmacodynamics of statin therapy, and consider the relevance of these findings to the efficacy of treatment, prevention of ADRs and what this may mean for patient tolerance and compliance.

2. Polymorphisms Affecting Statin Pharmacokinetics

Currently marketed statins are either dispensed in their prodrug lactone form (simvastatin and lovastatin) or the active acid form (atorvastatin, fluvastatin, pravastatin, rosuvastatin and pitavastatin).^[26] The lactone forms (prodrug forms) of statins are activated to their corresponding acid derivatives in the intestine by non-specific hydrolysis through carboxyesterases. The primary metabolism of statins, like the majority of all other drugs, is attributed to microsomal cytochrome

P450 (CYP) enzymes. The exception is pravastatin, which is transformed enzymatically in the liver cytosol. It has been demonstrated that the CYP450 isoenzyme CYP3A4 is the major route of metabolism of both statin-acid and lactone derivatives,^[27] and that both the acid form of statins as well as the acidic metabolite produced by CYP450 metabolism are responsible for the lipid-lowering effect achieved. CYP2D6 (fluvastatin, pitavastatin and rosuvastatin) and CYP2C9 (pitavastatin and rosuvastatin), in addition to CYP3A4, are also involved in the

metabolism of the above-mentioned statins. Cerivastatin, now withdrawn from the market, was reported to be metabolized by CYP2C8 in addition to CYP3A4. As statins undergo biotransformation through various CYP450 enzymatic pathways (figure 1), polymorphisms affecting particular CYP enzymes may affect the kinetic disposition of statin metabolites and resulting efficacy. In this review, SNPs are represented using their standard RefSNP (rs) nomenclature (where available) followed by the nomenclature that is commonly used in the literature.

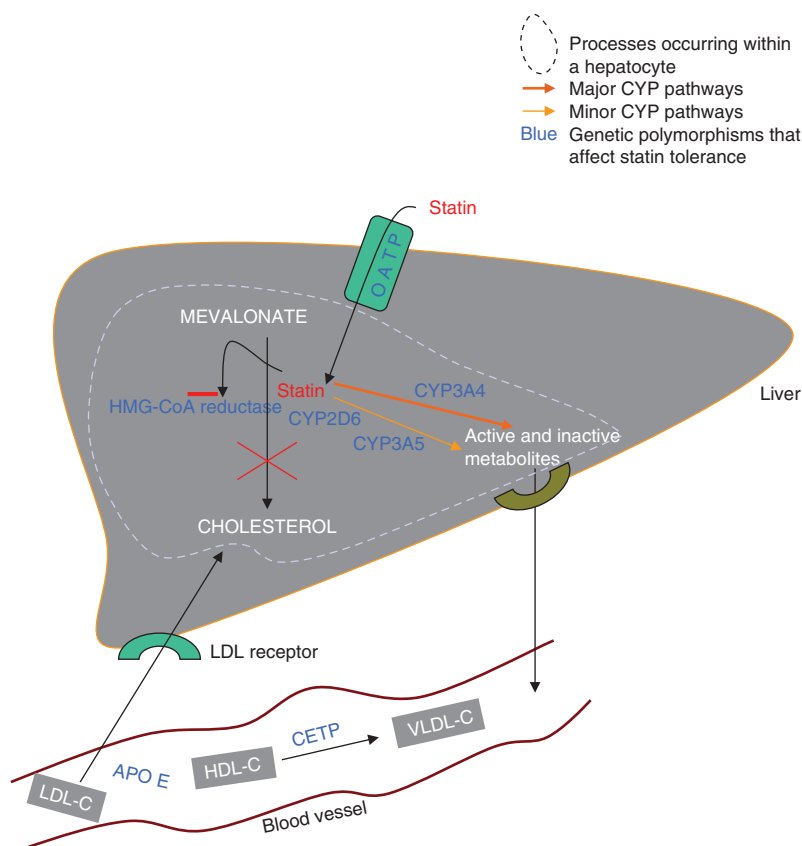


Fig. 1. Key molecular pathways of cholesterol synthesis and statin metabolism and disposition. Enzymes and transporters subject to genetic polymorphisms that affect the therapeutic response from statins are shown in blue. The statins (atorvastatin and simvastatin) are shown to be mainly metabolized by CYP3A4 and through minor pathways involving CYP3A5 and CYP2D6. The blood vessel depicted below the liver illustrates the apolipoprotein E (APO E) and cholesterol ester transfer protein (CETP) proteins, which are affected by genetic polymorphisms and are involved in lipid trafficking back to the liver. CYP=cytochrome P450; HDL-C=high-density lipoprotein cholesterol; LDL=low-density lipoprotein; LDL-C=LDL cholesterol; OATP=organic anion transporting polypeptide; VLDL-C=very low-density lipoprotein cholesterol.

2.1 Cytochrome P450 (CYP) 3A4

As stated, CYP3A4 is the main pathway via which statins (simvastatin, atorvastatin and lovastatin) undergo phase I metabolism. The activity of the *CYP3A4* gene can vary up to 10-fold between patients, therefore affecting the efficacy and tolerability of statin therapy.^[28] Furthermore, Kajinami et al.^[29] demonstrated that the expression of SNP rs2740574, better known as the *A-290G* variant in the *CYP3A4* promoter, resulted in a 12.4% increase in post-treatment LDL-C level compared with the wild-type allele. Additionally, in the same study, another SNP, rs4986910 (referred to as the *M445T* variant), resulted in enhanced efficacy with respect to LDL-C reductions following atorvastatin treatment (11.2–17.6%) compared with non-carriers, therefore suggesting this variant may result in a reduction in the metabolism of atorvastatin, with the resulting increase in plasma concentrations enhancing its efficacy.^[29]

Recently, a prospective study carried out in 423 patients of Chinese ethnicity investigated the variability in response to simvastatin and atorvastatin treatment, with a focus on *CYP3A4*1G* (no rs number available as *1 is a family of more than eight suballeles with minor variations), an intronic variant that occurs commonly in Asian populations.^[30] This study demonstrated a gene-dose-dependent effect of the *CYP3A4*1G* allele on the degree of lipid reduction after 4 weeks of treatment with atorvastatin, but not after simvastatin treatment.^[30] A null effect in patients prescribed simvastatin is surprising, as simvastatin is a prodrug requiring metabolism to its active compound (simvastatin hydroxyl acid). Therefore, it would be expected that patients with the *CYP3A4 *1G/*1G* would show a poor/no response, as the drug is not metabolized (opposite effect to atorvastatin). However, the lack of association is perhaps indicative of the degree to which CYP3A4 is differentially involved in simvastatin and atorvastatin metabolism.^[30]

2.2 CYP2D6

Pharmacogenetic studies have indicated that patients who are carriers of the *CYP2D6* homo-

zygous mutant alleles, rendering them poor metabolizers, demonstrate enhanced efficacy with respect to total cholesterol (TC) reduction with simvastatin treatment (0.23 mmol/L per mg of simvastatin) compared with patients possessing the wild-type genotype (*CYP2D6 wt/wt*) [0.10 mmol/L per mg of simvastatin].^[31] In this study, patients discontinuing statin treatment due to an adverse event were more prevalent in the *CYP2D6 mut/mut* group (80% discontinued treatment) compared with patients with the *CYP2D6 wt/mut* (46%) and *CYP2D6 wt/wt* (17%). That is, the decreased metabolism of simvastatin in poor metabolizers resulted in increased plasma concentrations of the drug and hence an increased lowering of TC, and therefore an increase in the risk of statin-associated ADRs (see table I for identification of specific SNPs involved).

ADRs have also been associated with the SNP rs3892097, referred to as the *CYP2D6*4* allele, the most common non-functioning variant of the *CYP2D6* enzyme.^[36] A proportion of patients who were prescribed atorvastatin therapy, and were reported to have experienced a muscle event, expressed the *CYP2D6*4* variant gene (50%). Muscle events noted were myalgia (defined in this case as muscle pain/ache without elevations in CK levels), myopathy (defined as muscle ache/pain, cramps with an elevation in CK levels) and rhabdomyolysis (defined as elevations in CK levels >10 × ULN). In the control group (i.e. those who were not prescribed atorvastatin therapy), 28% of individuals expressed the *CYP2D6*4* polymorphism.^[36]

2.3 CYP3A5

CYP3A5 is located very close to CYP3A4 and it is hypothesized that some effects are attributable to either gene.^[37] Individuals are expressers of *CYP3A5* if they carry at least one *1 allele, non-expressers do not have any *1 alleles and the *3 (rs776746) allele is referred to as the non-functional allele.

Kivistö et al.^[32] investigated the effect of a polymorphism in the *CYP3A5* gene on the metabolism and efficacy of lovastatin, simvastatin and atorvastatin in 69 Caucasian patients. These investigators demonstrated a 24% higher ($p=0.036$) plasma LDL-C level and 23% higher plasma TC

Table 1. Key studies investigating genetic factors that may alter the pharmacokinetics of statin metabolism

Gene (allele)	Study design; no. of pts; and statin(s) investigated	Main outcomes	Reference
<i>CYP3A4</i> (<i>A-290G</i> promoter- rs2740574) [<i>M445T</i> - rs4986910]	Randomized, double-blind, placebo-controlled study; 340 with primary hypercholesterolaemia; atorvastatin 10 mg/day	<i>A-290G</i> polymorphism was associated with a 12.4% increase in post-treatment LDL-C levels, hence decreased efficacy. In contrast, the <i>M445T</i> polymorphism was associated with enhanced efficacy shown through greater reductions in LDL-C levels	29
<i>CYP3A4</i> *1G (no rs number available as *1 is a family of >8 sub-alleles with minor variations)	Prospective cohort study; 217; atorvastatin 10 mg/day and simvastatin 20 mg/day	A 'gene dose-dependent effect' with respect to enhanced TC reduction in increasing order: <i>CYP3A4</i> *1/*1 (WT), <i>CYP3A4</i> *1/*G and <i>CYP3A4</i> *1G/*1G. This effect was only noted in pts prescribed atorvastatin	30
<i>CYP2D6</i> (genotypes identified and number of pts [x]) <i>CYP2D6</i> wt/wt (54) <i>CYP2D6</i> *3/wt (5) <i>CYP2D6</i> *3/*4 (1) <i>CYP2D6</i> *3/*5 (1) <i>CYP2D6</i> *4/wt (20) <i>CYP2D6</i> *4/*4 (2) <i>CYP2D6</i> *4/*5 (1) <i>CYP2D6</i> *4/2xN (1) <i>CYP2D6</i> *5/wt (3)	Hypercholesterolaemic pts referred to a lipid clinic; 88; maximal simvastatin dose of 40 mg/day	<i>CYP2D6</i> <i>mut/mut</i> genotypes are poor metabolizers and have a larger decrease in TC levels (0.23 mmol/L per mg of simvastatin) than pts possessing the WT genotype (<i>CYP2D6</i> wt/wt) [0.10 mmol/L per mg of simvastatin]	24
<i>CYP3A5</i> *3 (rs776746)	Case-control study; 263; atorvastatin (dose unknown)	Most common non-functioning variant, rs3892097 (<i>CYP2D6</i> *4), associated with muscle-related ADRs	31
	Prospective cohort study; 69; lovastatin or simvastatin (dose unknown)	Impaired efficacy in *3 expressers compared with *1 expressers. Also, this effect seems to be statin specific, as there was no efficacy alteration in statins not metabolized by <i>CYP3A5</i> (fluvastatin and pravastatin)	32
OATPs (SLCO1B1) rs2306283(c.388A>G) rs4149056(c.521T>C)	Pharmacokinetic study	221% increase in AUC values for simvastatin acid in pts expressing the <i>rs4149056</i> allele, 173% increased AUC value with pitavastatin, 144% with atorvastatin, 90% with pravastatin and 87% with rosuvastatin	33
	Genome-wide association study (SEARCH and HPS cohorts)	Relative risk of myopathy with the <i>rs4363657</i> SNP was 2.6 and 4.3 in the HPS and SEARCH cohorts, respectively	34
(<i>SLCO1B1</i> *15) [haplotype comprising c.521T>C and c.388A>G]	Case-control study; 10; pravastatin/simvastatin (dose unknown)	Significant ($p < 0.01$) association of <i>SLCO1B1</i> *15 with statin-associated myopathy attributed by elevations in creatine kinase	35

ADRs=adverse drug reactions; **AUC**=area under the plasma concentration-time curve; **CYP**=cytochrome P450; **HPS**=Heart Protection Study; **LDL-C**=low-density lipoprotein cholesterol; **mut**=mutant; **OATP**=organic anion transporting polypeptide; **pts**=patients; **rs**=RefSNP; **SEARCH**=Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; **SLCO**=solute carrier organic anion transporter; **SNP**=single nucleotide polymorphism; **TC**=total cholesterol; **WT**=wild type.

level ($p=0.0014$) 1-year post-treatment in patients who were *CYP3A5* expressers compared with patients homozygous for *CYP3A5**3 (non-expressers). The efficacy with respect to TC reduction was significantly ($p=0.026$) impaired by 17% when compared with patients who were homo-

zygous for *CYP3A5**3 (31% reduction in TC).^[32] In a further study, 139 patients who had been treated with atorvastatin 10 mg/day for 4 weeks were genotyped. Analysis of the *1D and non-functional *3C allele revealed a differential expression among patients of African descent (47.38% vs 55.2%,

respectively) compared with non-Africans (84.39% vs 84.8%).^[38] Subjects with the *3A haplotype (rs56244447), a combination of the *1D and *3C alleles, demonstrated significant ($p < 0.05$) impaired efficacy compared with non-*3A carriers.

Although the CYP3A5 enzymatic pathway may not be majorly involved in statin metabolism, the above cited literature suggests that genetic variation in *CYP3A5* may contribute to interindividual differences in response to some statins.

2.4 Organic Anion Transporting Polypeptides

Members of the membrane uptake transport proteins, specifically the organic anion transporting polypeptides (OATPs) or solute carrier organic anion transporters (SLCOs), are important for drug uptake and hence the response to a drug. These transporters are expressed in the liver, intestine and parts of the CNS.^[39] Several studies have investigated the effect of genetic polymorphisms involving these transport pumps and the resulting pharmacokinetics of statin therapy. Most frequently discussed polymorphisms include the *SLCO1B1* gene that encodes the 1B1 (OATP1B1) influx transporter and has two main variants [rs2306283(c.388A>G) and rs4149056(c.521T>C) SNPs], which affect transporter function with respect to statin transport.^[40] However, the effects on transporter function are dependent on the individual combination haplotypes. For example, the rs2306283(c.388A>G) haplotype is associated with increased OATP1B1 activity and lower statin concentrations in the plasma.^[41] In comparison, the c.521T>C SNP is associated with reduced transporter activity and therefore increased plasma concentrations of statins.^[42] Although all statins are substrates of the OATP1B1 transporter,^[43,44] the effect of *SLCO1B1* polymorphisms has been demonstrated to affect patients on simvastatin particularly.^[33] Based on area under the plasma concentration-time curve (AUC) analysis, exposure to simvastatin acid (active form) was 221% greater in patients homozygous for the rs4149056 allele (c.521CC) compared with patients expressing the c.521TT allele.^[33] Further AUC analyses for other statins demonstrated a 173% increase in AUC values for pitavastatin,

144% for atorvastatin, 90% for pravastatin and 87% for rosuvastatin.^[33,42,43,45,46]

With respect to ADRs, publication by the SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) Collaborative Group identified the *SLCO1B1* c.521T>C SNP as being associated with simvastatin-induced myopathy.^[34] This SNP was discovered through a genome-wide association study (GWAS) involving over 300 000 candidate genes in 85 confirmed cases of statin-induced myopathy and 90 controls from the SEARCH cohort of patients. This was then replicated in a cohort of just under 20 000 patients from the HPS (Heart Protection Study). In the HPS, 23 confirmed cases of myopathy were identified as being significantly ($p = 0.004$) associated with rs4363657. Furthermore, the relative risk of myopathy with the rs4363657 SNP was 2.6 and 4.3 in the HPS and SEARCH cohorts, respectively.^[34]

Since publication of this data, further GWAS reviews into the above SNPs have been undertaken and several cohorts of patients on statin therapy have now been genotyped and are being investigated for a link with reported *SLCO1B1* polymorphisms and their association with statin-induced myopathy. Lang et al.^[47] genotyped over 4000 patients enrolled in the GO DART (Genetics of Diabetes Audit and Research in Tayside) study for the rs2306283 and rs4149056 SNPs. The homozygous TT allele was associated with a 3-fold increase in statin intolerance. Also, patients with the TT allele were less likely to achieve the treatment target LDL-C level of 2 mmol/L. In the STRENGTH (Statin Response Measured by Genetic Haplotype Markers) study, the rs4149056 SNP was associated with a significant number of patients discontinuing the trial for any adverse effect, including discontinuing the trial for myalgia (with no reported increases in CK).^[48] Furthermore, a gene-dose effect was observed, that is, patients with no, one and two alleles had a 19%, 27% and 50% trend to reporting an adverse event, respectively.^[48] A smaller study comprising ten patients with myopathy, diagnosed as an abnormal elevation in CK, and 26 patients with normal CK levels following statin treatment, revealed a

significant ($p < 0.01$) association between myopathy and the presence of the *SLCO1B1**15 allele (haplotype comprising c.521T>C and c.388A>G) in patients prescribed either pravastatin or atorvastatin.^[35] This haplotype is reported to decrease hepatocellular transport and therefore increase the systemic exposure of specific drugs, and hence is more likely to affect the response to pravastatin treatment due to its metabolic profile.^[49,50]

2.5 Co-Enzyme Q10 and Statin-Associated Myopathy

Mechanisms for statin-associated hepatotoxicity and myopathies are not well established. However, the depletion of cholesterol within the myocyte cell wall and/or the depletion of key intermediates synthesized in the cholesterol biosynthetic pathway are hypothesized as possible causes of myopathy.^[51] A well discussed hypothesis regarding myopathies refers to the depletion of a particular enzyme involved in the cholesterol biosynthetic pathway: ubiquinone, more commonly referred to as co-enzyme Q10 (CoQ10).^[51] CoQ10 is an essential antioxidant that is regenerateable and crucial for the oxidative phosphorylation process, which generates adenosine triphosphate (ATP) necessary for the functioning of all cellular processes.^[52] Investigations are yet to establish that decreased CoQ10 enzyme levels as a result of statin therapy directly co-relate with the symptoms of myopathy. However, a study has shown that CoQ10 enzyme levels were significantly ($p < 0.05$) lower in statin-treated patients (0.75 ± 0.04 mg; $n = 40$) compared with untreated hypercholesterolaemic patients (0.95 ± 0.09 mg; $n = 20$).^[53] Further studies investigating the association of plasma CoQ10 levels and myopathy are well reviewed in a recent publication.^[54]

Mutations in the *COQ2* gene are also associated with severe inherited myopathy.^[55] Oh et al.^[56] hypothesized that common variations in the *COQ2* gene would be associated with statin-associated myopathy. 133 patients who had previously developed statin-associated myopathy (clinically established) and 158 matched controls were genotyped for three variants referred to as SNP1, SNP2 and 2-SNP, the haplotype of SNP1 and SNP2. All

three variants showed significant associations with statin-associated myopathy, as represented through ORs of 2.42, 2.33 and 2.58 for SNP1, SNP2 and 2-SNP, respectively.^[56] Further studies into statin-associated myopathy with respect to the *COQ2* gene have not been followed up or replicated in another cohort to date.

3. Polymorphisms Affecting the Pharmacodynamics of Statins

The preceding section discussed polymorphisms in genes that code for proteins involved in the metabolism and/or transport of statins, therefore influencing their pharmacokinetics and resulting efficacy. Section 3 focuses on genes that code for proteins involved in the mechanism of action of statins, and therefore influence pharmacodynamic processes. This type of variation will not affect drug metabolism or transport, and therefore will not impact on plasma or tissue levels of the drug. Section 3 also discusses genes that code for proteins associated with the development of CHD or its intermediate phenotypes of hypercholesterolaemia. Examples of genetic variants of relevance to statin pharmacodynamics are discussed below.

3.1 Adenosine Triphosphate-Binding Cassette Transporters and CYP7A1

The ATP-binding cassette (ABC) transporters G5 and G8 are involved in intracellular cholesterol transport and hence homeostasis of intracellular cholesterol biosynthesis. The *CYP7A1* gene encodes the 7α -hydroxylase enzyme, which is the rate-limiting step in the bile acid synthesis pathway for cholesterol.^[57,58] 337 patients treated with atorvastatin 10 mg for 36 weeks were genotyped for the *ABC* G5 and G8 polymorphisms, as well as a variant promoter (*A-204C*) in the *CYP7A1* gene. Results from the investigation revealed that the rs11887534 SNP, commonly referred to as the *D19H* variant in the *ABC* G8 allele, was significantly ($p = 0.043$) associated with a larger fall in LDL-C levels compared with wild-type allele homozygotes (39.6% compared with 36.6%, respectively). In contrast, patients

not carrying the rs3808607 SNP, referred to as the *A-204C* promoter variant, had significantly ($p=0.048$) enhanced efficacy with respect to a greater (42.7%) reduction in LDL-C levels compared with carriers (38.2%).^[58] This is supported by investigations by Takane and colleagues,^[59] who also demonstrated that patients with the *A-204C* promoter variant treated with pravastatin demonstrated significantly reduced efficacy with respect to lowering LDL-C (24.3%) compared with non-carriers (33.1%). Furthermore, another study comprising 324 patients demonstrated the effect of this promoter polymorphism (*A-204C*) in response to treatment with atorvastatin 10 mg/day for 52 weeks. The reduction in LDL-C was significantly affected (34%; $p<0.0001$) in female patients homozygous for the promoter polymorphism, compared with a 39% and 37% reduction in wild-type and heterozygous patients, respectively.^[60] Additionally, male patients homozygous for the *CYP7A1 A-204C* promoter polymorphism and who carried the *E4 Apo E* allele had a smaller reduction in LDL-C compared with male patients who were carriers of the *E2* or *E3* allele. This observation is unique, as it describes an additive effect of genetic variants resulting in a poorer response to statin treatment when two specific polymorphisms were present.^[60]

3.2 P-Glycoprotein

Another class of ATP-dependent efflux pumps implicated in variable response to statins is P-glycoprotein (P-gp). One of the main features of this efflux pump is its broad substrate specificity and the ability to regulate the distribution, and hence bioavailability, of various drugs.^[61,62] Lovastatin, simvastatin and atorvastatin have been described as inhibitors of P-gp.^[63] The P-gp efflux pump is known to transport many therapeutic drugs from the gastrointestinal tract to the circulation (antineoplastics, calcium channel antagonists, statins, antibacterials, anticonvulsants and others).^[64] Thus, inhibition of the P-gp efflux pump by statins may lead to reduction in efflux back into the gut during absorption and therefore an increase in absorption of these drugs transported by this pump, which may result in reduced

efficacy or ADRs due to altered drug translocation and accumulation.^[65,66] With respect to genetic polymorphisms affecting lipid levels, P-gp is coded through the *ABCB1 (MDR-1)* gene, and allelic variants of this gene are known to affect the response to statin treatment.^[67] 344 patients treated with atorvastatin 10 mg/day for 52 weeks were genotyped for two polymorphisms in the *ABCB1* gene. The presence of the rs1045642 SNP, commonly referred to as the *3435T* homozygous variant, in females was significantly associated with reduced efficacy with respect to LDL-C reduction and a moderate increase in high-density lipoprotein cholesterol (HDL-C).^[67]

A further study incorporating 116 hypercholesterolaemic patients treated with simvastatin 20 mg/day for 6 months investigated the effects of genetic polymorphisms in the *ABCB1*, *CYP3A5* and *CYP3A4* genes and their effect on the response to statin treatment.^[68] Results indicated that patients who were carriers of the *ABCB1 1236T* variant allele (rs1128503) demonstrated significantly ($p=0.042$) enhanced efficacy with respect to reduction in plasma TC (29%) and LDL-C (39.6%) levels compared with patients carrying the wild-type allele (24.2% and 33.8%, respectively).^[68] In this study, no significant associations with statin efficacy were related to polymorphisms in the *CYP3A5* and *CYP3A4* genes.^[68]

The altered efficacy observed in above-mentioned studies is supported by a Finnish study that investigated the effects of three commonly occurring *ABCB1* haplotypes on the pharmacokinetics of statins in 24 healthy patients. The three SNPs genotyped were *1236C>T* (rs1128503), *2677G>T/A* (rs2032582) and *3435C>T* (rs1045642).^[69] Patients with the homozygous TTT haplotype had a significantly ($p=0.039$) greater (60%) AUC value for the active metabolite, simvastatin acid, compared with patients who had the homozygous CGC haplotype.^[69] This result was replicated with atorvastatin where patients with the homozygous TTT haplotype had a significantly ($p<0.025$) greater (55%) AUC value compared with the homozygous CGC haplotype. Also, a 24% longer half-life was associated with the homozygous TTT haplotype compared with patients who had the homozygous CGC haplotype.^[69] Therefore, this supports the observa-

tions of enhanced efficacy in the studies discussed above.

3.3 Apolipoprotein E

Apolipoprotein E protein (Apo E) binds to lipids and lipoprotein receptors, and modulates lipoprotein levels by influencing the clearance rate, lipophilic conversion and very low-density lipoprotein (VLDL) and triglyceride production.^[70] The human *Apo E* gene may be expressed as one of three alleles: *E2*, *E3* (wild type) and *E4* in order of increasing affinity for the LDL receptor.^[23]

Specific genes can code for proteins associated with the development of CHD or its intermediate phenotypes, such as hypercholesterolaemia. Specific polymorphisms in the *Apo E* gene have been associated with the development of MI in a cohort of patients on a high-fat diet.^[71] As may be expected, high saturated fat intake was associated with a 49% increase in the risk of MI in patients with the wild-type genotype (OR = 1.49). However, the risk of MI was compounded with the *Apo E2* and *E4* variants, which in addition to saturated fat intake were associated with a 2.2-fold (OR = 3.17) and 1.6-fold (OR = 2.59) increase in the risk of MI, respectively.^[71] A prospective investigation of the ARIC (Atherosclerosis Risk in Communities) cohort also demonstrated that both Whites and African Americans with the *E2* variant had significantly ($p = 0.006$) higher HDL-C, lower LDL-C ($p < 0.0001$) and lower carotid intima-media thickness ($p = 0.009$) compared with patients with the *E3* homozygous variant.^[72] In contrast, carriers (of both ethnicities) of the *E4* variant had lower HDL-C level, higher LDL-C level and higher intima-media thicknesses. However, when adjustments were made for other factors such as sex, weight, smoking, diabetes mellitus and hypertension, there was no association of development of CHD with respect to the *Apo E* allele.^[72] Furthermore, genotype data from the GO DART study comprising approximately 1300 patients demonstrated *Apo E* variants were associated with impaired statin efficacy with respect to 32% of patients with the *E4* variant not reaching treatment target levels for LDL-C (i.e. 2 mmol/L) compared with all patients who expressed the *E2* variant meeting this target.^[73]

Other studies investigating variants of *Apo E* have indicated that the *Apo E4* allele is associated with a decreased response to statins compared with the *Apo E2* allele, which is present more frequently in responders.^[74] A decreased compliance with statin therapy of 2.3-fold was noted in *Apo E4* carriers, which may be associated with a poor response to statin therapy or statin-associated adverse effects.^[74] Regarding fluvastatin therapy, the *Apo E 3/3* genotype has been attributed to enhanced efficacy with respect to reductions in plasma TC (20.4% vs 15.4%; $p = 0.01$) and LDL-C (28.7% vs 22.7%; $p = 0.03$) compared with *Apo E 3/4* or *4/4* genotypes.^[75] Furthermore, patients with the *Apo E 2/3* genotype had a greater increase in HDL levels (19.1% vs 4.3%; $p = 0.002$) in response to fluvastatin therapy than those with genotypes *3/3*, *3/4* and *4/4*.^[75]

Further investigations into *Apo E* variants associated with variable response to statin treatment include a study comprising 328 males and females treated with atorvastatin 10 mg for 1 year. Before the initiation of treatment, both male and female groups had similar baseline lipid profiles. Males with the *E2* allele showed significantly enhanced efficacy with respect to reductions in LDL-C (44%; $p = 0.021$), TC (34%; $p = 0.033$) and triglyceride levels (27%; $p = 0.049$) compared with patients with the *E3* or *E4* alleles.^[76] However, the greater efficacy of statins in carriers of the *E2* allele was shown to be non-significant in an outpatient study comprising 401 males and females assigned to pravastatin 20 mg/day for 16 weeks.^[77] This study showed that when factors such as body mass index, age and sex were taken into consideration the *Apo E* genotype was not associated with variable response to pravastatin treatment.^[77] In another study in 116 patients treated with atorvastatin or bezafibrate for 1 year, carriers of the *Apo E* promoter region polymorphism $-491T$ (*Apo E4*) allele showed a significantly ($p = 0.037$) greater reduction in LDL-C level (35%) than non-carriers (27%). In contrast, patients on bezafibrate treatment with the $-491T$ allele showed a significantly ($p = 0.05$) reduced efficacy with respect to modification of triglycerides (reduced by 23%) compared with non-carriers (39%).^[78]

3.4 Cholesteryl Ester Transfer Protein

Another genetic polymorphism, often associated with variation in statin response, is the cholesteryl ester transfer protein (CETP).^[18,22] CETP is involved in the transport of cholesteryl ester back into the liver and functions to transport triglycerides from LDL and VLDL to HDL.^[22] A polymorphism in the first intron of the *CETP* gene is referred to as *TaqIB* (rs708272); the presence of this restriction site, referred to as the *B1* allele, results in the carrier having elevated CETP concentrations and hence lower HDL-C levels. Furthermore, carriers of the *B1B1* homozygous allele of *CETP* are reported to develop coronary atherosclerosis at an accelerated rate compared with wild-type carriers.^[79] Further research by van Venrooij and colleagues^[80] evaluating polymorphisms of *CETP* in response to atorvastatin 10 or 80 mg/day in 217 diabetic patients revealed similar results. In this study, patients with the *B1B1/CC* polymorphism had a more atherogenic lipid profile at baseline and responded well to atorvastatin therapy, with a 7.2% increase in plasma HDL-C compared with increases of 6.1% and 0.5% in carriers of the *B1B2* and *B2B2* *CETP* variants, respectively.^[80] The *B2B2* genotype, which was associated with only a 0.5% increase in plasma HDL-C levels, was associated with elevated HDL-C levels at baseline in the WOSCOPS (West Of Scotland Coronary Prevention Study) study and was associated with a 30% decreased risk of a cardiovascular event compared with *B1B1* homozygotes.^[81]

Furthermore, a recent meta-analysis comprising nearly 14000 patients revealed a significant association between the *TaqIB* genotype and HDL-C levels.^[82] Patients with the *B2B2* homozygous allele had significantly increased HDL-C levels of 0.11 mmol/L ($p < 0.0001$) compared with patients with the *B1B1* genotype. However, this study did not show any association between patient allelic type and the response to pravastatin treatment. Also, the efficacy of pravastatin therapy, defined as the OR of developing coronary artery disease, was not associated with the *TaqIB* polymorphism.^[82] Further studies of a cohort of 812 patients with coronary artery disease from REGRESS (the Regression Growth Evaluation

Statin Study) have shown similar results.^[83] Patients treated with pravastatin 40 mg/day for 2 years were genotyped for various *CETP* variants. Patients expressing the *B2* variant had significantly ($p < 0.001$) decreased plasma CETP levels and increased HDL-C levels compared with non-carriers.^[83] Also, after a 10-year follow-up period, carriers of the *B2* variant had an elevated risk of both endpoints (MI and death from ischaemic heart disease). The 10-year absolute risk of mortality was 5% in patients expressing the *B1B1* variant, 8% in *B1B2* expressers and 15% in *B2B2* expressers.^[83]

A further study investigating over 2500 patients who had undergone coronary arteriography were genotyped for *CETP* variants^[84] and followed up to assess outcomes of MI and mortality. Treatment with statins was determined through patient interview and health record systems. As expected, patients treated with statins had an overall reduced event rate (21.5%; $p = 0.006$) compared with untreated patients (26.7%). With respect to *CETP* variants, statin-treated patients with *B1B2* or *B2B2* variants had significant reductions in event rates (21% and 17.4%, respectively) compared with non-treated patients (28% and 26.4%, respectively).^[84] Furthermore, in untreated patients expressing the *B1B1* variant there were fewer events of MI or mortality (24.8%) compared with *B2B2* expressers (27.6%); however, this observation was not significant.^[84] With specific respect to mortality, statin treatment, when compared with untreated patients, significantly reduced mortality in patients with the *B1B1* variant by 30% (from 13.8% without statin treatment to 9.7% with statin treatment), *B1B2* by 42% (16.9% to 9.8%) and *B2B2* by 68% (16.4% to 5.3%).^[84]

3.5 HMG-CoA Reductase Enzyme

Statins are competitive inhibitors of the HMG-CoA enzyme, the rate-limiting step for the biosynthesis of cholesterol within hepatocytes.^[27] The HMG-CoA reductase gene is polymorphic and variants of this gene alter the rate of cholesterol biosynthesis and lead to variability in the response to statin therapy.^[85]

In a study of the effect of allelic variants of the HMG-CoA reductase gene (*HMGCR*), DNA from

1536 patients treated with pravastatin 40 mg/day was collected and analysed for 148 SNPs across ten genes involved in lipid metabolism. *SNP 12* (rs17244841) and *SNP 29* (rs17238540) were identified as affecting the variability of statin responsiveness and occurred in approximately 6.7% of the study population. *SNP 12* and *SNP 29* are in tight linkage with one another (can be said to be equivalent to each other) and are commonly expressed in equal frequencies. The two SNPs were attributed to reductions in efficacy of statins with respect to reduction in TC lowering by up to 22% and LDL-C lowering by up to 19% ($p=0.001$) compared with patients who had neither haplotype.^[85] A further investigation showed that 29% of patients from the GO DART study who were genotyped for *SNP 29* demonstrated a failure to reach lipid-lowering targets if they were carriers of the more frequent T allele compared with 51% of patients with a single copy of the less frequent G allele.^[86] Furthermore, heterozygous patients (T allele/G allele [TG]) had significantly reduced efficacy with respect to lowering TC (-32.3% vs -37.1%) and triglyceride levels (-27.5% vs -37.6%).^[86]

A further study investigated the response to 6 weeks of treatment with simvastatin 40 mg/day, and the response in 326 African American men compared with the response in 596 Caucasians. African American men with haplotype 7 (*H7*), defined by the *SNP 12*, *SNP 29* and *SNP 20144* polymorphisms, had a significantly ($p=0.0009$) reduced response to simvastatin in terms of LDL-C reduction compared with those in the population without this haplotype.^[25] Furthermore, African American men carrying the *H7* and/or *H2* (combination of 11 SNPs within the *HMGCR*) haplotypes had a significantly lower reduction ($p=0.001$) in LDL-C (28.2%) compared with carriers of either *H7* or *H2*, who on average had a 41.5% reduction in LDL-C. Once again, 11 of 12 patients who had the *H7* and/or *H2* haplotypes were of African American origin.^[25]

3.6 Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)

Statins induce the expression of sterol regulatory element-binding protein-2 (SREBP-2), a

transcription factor that activates the *proprotein convertase subtilisin/kexin type 9* (*PCSK9*) gene, which in turn encodes a protein that regulates (via degradation) the number of cell surface LDL receptors.^[87] Since statins inhibit HMG-CoA reductase, indirectly upregulate the expression of LDL receptors and hence enhance LDL-C clearance from the plasma, a polymorphism in *PCSK9* may vary a patient's response to statin treatment. Berge et al.^[88] investigated this by genotyping 38 hypocholesterolaemic patients. Results revealed that 16% (six patients) of patients were heterozygous for a *PCSK9* polymorphism. To evaluate this further, 441 severely hypercholesterolaemic patients were genotyped and results revealed that none of these patients had the *PCSK9* polymorphism. Comparing the two groups revealed that the *PCSK9* polymorphism was significantly ($p<0.0001$) associated with hypocholesterolaemia.^[88]

Furthermore, in two separate cohorts of patients with familial hypercholesterolaemia, a proportion of those who responded well to statin treatment were heterozygous for the *PCSK9* polymorphism.^[88] The authors of this study stress the importance of classifying the polymorphisms as either gain-of-function polymorphisms or loss-of-function polymorphisms. These are likely to have opposite effects on patients' response to statin therapy.

With respect to polymorphisms either causing a loss of function or a gain of function, an *in vitro* study in HepG2 cells investigated the effect of four loss-of-function polymorphisms of the *PCSK9* gene and two gain-of-function polymorphisms of the *PCSK9* gene and their effect on the enzyme coded by the gene. The two groups of polymorphisms did not differ with respect to the degree of catalytic activity of the enzyme produced by *PCSK9*, though the four loss-of-function polymorphisms resulted in a 16% increased expression of LDL receptor as well as a 35% increased internalization of LDL receptors compared with wild-type *PCSK9*. In contrast, the two gain-of-function polymorphisms resulted in a 23% reduction in LDL receptor expression as well as a 38% decreased level of receptor internalization.^[89] As previously discussed (section 3.6), statin efficacy is achieved through the indirect up-regulation of

LDL receptors. Therefore, loss-of-function or gain-of-function variants affecting LDL-receptor expression are expected to affect statin efficacy.

PCSK9 knockout mice administered a diet comprising 0.2% lovastatin showed an enhanced reduction in plasma TC (20% decrease) compared with wild-type mice (12% decrease), but no significance data were provided.^[90] Knockout mice also had a 2.8-fold elevated LDL receptor expression compared with wild-type mice. Lovastatin administration increased LDL-receptor expression to 4.6-fold in knockout mice compared with wild-type mice. These observations *in vitro* and *in vivo* suggest an important role for the *PCSK9* gene, and for polymorphisms affecting this gene, in lipid metabolism and in the response to statin therapy.

3.7 Atrogin-1

Atrogin-1 is a protein ligase from the ubiquitin proteasome pathway and has been known to be induced during the early phases of muscle atrophy.^[91,92] Animal studies have shown that *atrogin-1* knockout mice do not develop muscle atrophy, suggesting that it is a key mediator in protein degradation.^[93] In an *in vivo* study using cultured myotubes, application of lovastatin resulted in a dose-dependent decrease in myotube size and morphology that correlated with an increased expression of atrogin 1.^[93] Similarly, a human study using muscle biopsies from eight patients being treated with statins showed a significant ($p=0.017$) 2-fold elevation in atrogin-1 expression levels compared with five patients with muscle pain not taking statins and six control patients.^[93] Studies incorporating a larger cohort of patients will further help in understanding the link between atrogin-1 and statin-induced myopathy. See table II for a summary of section 3.

4. Summary

As with 80% of all clinically used drugs, the statins undergo phase I metabolism via the CYP450 enzymatic pathways, which comprise the polymorphic genes *CYP2D6*, *CYP3A4* and *CYP3A5*. It would be expected that variations in

expression patterns (over-expression or expression of inactive enzymes) would play a large role in statin efficacy. To some extent, this is true, as the expression of the CYP3A5 enzyme is associated with a reduced response to statin therapy. Additionally, specific variation(s) in one or more of these CYP450 enzymes alters the rate at which statins are metabolized in the liver and hence alters their pharmacokinetic profile, as discussed in section 2. These changes, as a result of varying plasma concentrations of active metabolites, influence the therapeutic effects of statin therapy. Specific polymorphisms in the CYP450 enzymes, resulting in differences in plasma concentrations of active metabolites, have also been demonstrated to contribute to ADRs associated with statin therapy, such as muscle pain and, in severe cases, myopathy.

Although CYP450 enzymes are involved in 80% of all phase I metabolism of clinical drugs, and to a large extent that of statins (except pravastatin), one of the most critical findings with respect to variability in statin response has been the association of specific *SLCO1B1* variants and resulting statin-associated myopathy. Physicians are often at a loss when muscle complaints (myalgias) not confirmed with elevations in CK levels occur after initiating statin treatment or an increase in statin dose. *SLCO1B1* variants have been shown to be associated with an increased risk of myalgias and myopathy, with investigations in a large-scale GWAS as well as laboratory evidence indicating that these variants alter the pharmacokinetics of statin metabolites as shown through AUC analysis (section 2.4).^[34,48,94,95] However, testing for this particular variant prior to initiating statin therapy has not yet been considered or investigated through cost-benefit analysis. Perhaps further large-scale cohort investigations that definitively confirm the association of specific polymorphisms in the *SLCO1B1* variants with statin-associated myopathy should induce researchers to consider implementation of genetic testing prior to the initiation of statin therapy.

Regarding pharmacodynamics, the *Apo E* gene has been extensively discussed in the literature with respect to associations with CVD development, as well as response to statin therapy.

Table II. Key studies investigating genetic factors that may alter pharmacodynamics of statin metabolism

Gene (allele)	Study design; no. of pts; and statin(s) investigated	Main outcomes
Apolipoprotein genotype	Case-control study; ^[75] 320; fluvastatin 40 mg/day or placebo	The <i>Apo E</i> 3/3 genotype was significantly associated with a greater reduction in TC and LDL-C levels (20.4% and 28.7%, respectively) than the <i>Apo E</i> 3/4 or 4/4 alleles (15.4% and 22.7%, respectively). Also, pts with the <i>Apo E</i> 2/3 allele had a greater increase in HDL-C levels (19.1%) than pts with the 3/3, 3/4 or 4/4 (4.3%) allele
–491T promoter region polymorphism	RCT ATOMIX study ^[78] ; 116; atorvastatin (10–40 mg) or bezafibrate (400 mg)	Atorvastatin-treated group expressing the –491T promoter region polymorphism showed significantly enhanced efficacy with respect to reductions in LDL-C levels (35%) compared with non-carriers (27%). An opposite effect was noticed in the bezafibrate-treated pts. Carriers of the –491T polymorphism in this treatment group showed significantly impaired efficacy with respect to reductions in triglyceride levels (23%) compared with non-carriers (39%)
P-glycoprotein <i>ABCB1</i> (3435T) rs1045642	Placebo-controlled RCT; ^[67] 344; atorvastatin 10 mg/day	Females homozygous for the 3435T polymorphism had significantly lower reductions in LDL-C levels and increased HDL-C levels post-statin treatment
1236T and 2667A/T rs1128503	Prospective study; ^[68] 116; simvastatin 20 mg/day	Pts heterozygous for the 1236T polymorphisms had an enhanced efficacy with respect to reductions in TC (29%) and LDL-C (39.6%) compared with pts who were homozygous or non-carriers (24.2% and 33.8%, respectively). Additionally, pts with the 2667A/T polymorphism showed similar significant results
CETP <i>Taq1B</i> (rs708272) [B1B1, B1B2, B2B2]	Case-control study; ^[84] 2531; various statins used by pts	Significant reduction in CV event rates in pts treated with statins and expressing the B1B2 or B2B2 variants compared with B1B1 expressers. Untreated pts expressing the B1B1 genotype had fewer CV events compared with pts expressing B2B2
HMG-CoA reductase <i>SNP 12</i> (rs17244841) <i>SNP 29</i> (rs17238540)	Community-based randomized trial and cohort study; ^[85] 1536; pravastatin 40 mg/day	Pts who were carriers of either <i>SNP12</i> or <i>SNP29</i> had significantly lower reductions in TC and LDL-C by up to 22% and 19%, respectively, compared with pts without the above-mentioned SNPs
	Prospective cohort study; ^[25] 326 African American men and 596 Caucasian men; simvastatin 20 mg/day	African American men with the <i>H7</i> haplotype had a significant reduction in efficacy with respect to LDL-C level reduction compared with non-carriers. <i>H7</i> was not significantly associated with a reduction in efficacy in the Caucasian population. Also, African American men with both the <i>H7</i> and <i>H2</i> haplotypes had a significantly lower reduction in LDL-C levels (28.2%) than pts carrying only one haplotype (41.5%). This effect was not prevalent in the Caucasian population

Apo E=apolipoprotein E; **ATOMIX**=atorvastatin in mixed dyslipidaemia; **CETP**=cholesteryl ester transfer protein; **CV**=cardiovascular; **HDL-C**=high-density lipoprotein cholesterol; **LDL-C**=low-density lipoprotein cholesterol; **pts**=patients; **RCT**=randomized controlled study; **rs**=RefSNP nomenclature; **SNP**=single nucleotide polymorphism; **TC**=total cholesterol.

However, the variation in results discussed in section 3.3 when lifestyle factors are taken into consideration is noteworthy. Therefore, it is plausible to suggest that identifying key variants of the *Apo E* gene responsible for increased risk of CVD development, as well as impaired statin response, needs to be researched further. Two other important polymorphic genes discussed

with respect to variation in the pharmacodynamic response to statin therapy are the CETP protein (section 3.4) and the *HMG-CoA reductase* gene (section 3.5).

Taq1B (rs708272) variants of the *CETP* gene have been associated with decreased plasma HDL-C levels as well as variable response to statin therapy (section 3.4). It is well established

that increasing plasma levels of HDL-C are inversely related to the incidence of CHD and stroke. However, identifying patients with *CETP* variants that are associated with lower HDL-C levels (*B1B1* variant) and who will benefit more from statin treatment than would those with the *B2B2* variant, has therefore identified *CETP* variants as a polymorphic gene to consider before initiating statin therapy.

Recently, torcetrapib was developed to selectively target and inhibit *CETP* production and therefore raise HDL-C levels, which it did by 61%.^[96] However, the ILLUSTRATE (Atherosclerosis by *CETP* inhibition and HDL elevation) trial was prematurely ended due to an increase in the reports of death, angina, MI, revascularization procedures and heart failure in the cohort of patients receiving torcetrapib plus atorvastatin compared with patients receiving only atorvastatin,^[97] perhaps suggesting that inhibition of *CETP* may not entirely be beneficial even though this raises HDL-C levels significantly.

Considering that the HMG-CoA reductase enzyme is the rate-limiting step in the endogenous synthesis of cholesterol, as well as being the target of statin therapy, it is plausible that statin efficacy would be greatly affected by variations in the expression patterns of the HMG-CoA reductase enzyme (section 3.5). As cholesterol synthesis occurs through the mevalonate pathway, investigations are now looking into variants of various enzymes in the entire pathway rather than just the rate-limiting step,^[98] with key molecular pathways of cholesterol synthesis and statin metabolism and disposition shown in figure 1. The *PCSK9* gene (section 3.6) and atrogen-1 protein (section 3.7) are also discussed with reference to altering response to statin efficacy. Atrogen-1 in particular has recently been implicated as being linked with statin-associated myopathy. However, largely animal studies have investigated atrogen-1 and no clinical trials or human cohorts have been investigated

5. Conclusions

At present, over 120 drugs include pharmacogenetic information on their drug labels that

state that a test is *required* (e.g. trastuzumab – confirmation of *HER2/NEU* over-expression). In other cases a test is *recommended* (e.g. in 2007, the US FDA recommended that patients of Asian descent be genotyped for the *HLA-B*502* allele, as it has been associated with carbamazepine-induced Stevens-Johnson syndrome or toxic epidermal necrolysis in this particular ethnic group). In further cases it is suggested that pharmacogenetic information is provided (celecoxib, tamoxifen, isoniazid and others).^[99,100] The FDA has approved six *in vitro* pharmacogenetic tests for five drugs (warfarin – *CYP2C9* and *VKORC1*; irinotecan – *UGT1A1*; voriconazole, atomoxetine and tamoxifen – *CYP2C19* and *CYP2D6*).^[101] There are also a number of private laboratories offering commercial pharmacogenetic testing for the above-mentioned drugs and more, which can cost anywhere between \$US250 and \$US500 per test (year value 2007), and costs are often not covered by the US medical insurance schemes unless deemed necessary.^[102]

Pharmacogenetics and its application in medicine to individualized drug therapy have been shown to be clinically and economically beneficial in quality-adjusted life-year assessments.^[103,104] Therefore, polymorphisms affecting the pharmacokinetic and pharmacodynamic profiles of statins, which are widely used in therapy, with their potential application in the personalized prescribing of statin therapy, needs further research. For pharmacogenetic studies this will require large numbers of patients who have been exposed to statins and have experienced adverse outcomes, as well as control groups who have been exposed without experiencing adverse outcomes. It is feasible to link pharmacogenetic investigations with national pharmacovigilance databases to carry out such research.^[105] It is difficult to set a timeline for this as the field of pharmacogenetic testing continues to grow at an exponential rate. However, it could be possible that further cumulative evidence will reinforce the benefit of predictive genotyping to personalize dosing and hence further improve the outcome of statin therapy in patients who are intolerant to certain drugs or experience ADRs.

In this article we have reviewed specific polymorphisms that may affect the variability in re-

sponse to drugs, with a focus on statin therapy. It is also important to note that in some of the literature discussed, different ethnic groups have been demonstrated to have different allele frequencies for many of the genetic polymorphisms involved in variations in statin response. Investigations of the effects of ethnic differences in relation to polymorphisms affecting statin therapy are required. A multi-gene/haplotype approach needs to be applied in prospective studies using large cohorts of patients to establish the association of the various genetic polymorphisms with variability in statin response, including the propensity for ADRs.

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