




REVIEW ARTICLE



Personalised medicine in hypercholesterolaemia: the role of pharmacogenetics in statin therapy

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ABSTRACT

Statins are the first-line choice in Lipid-lowering therapy to reduce cardiovascular risk. In a continuous attempt to optimise treatment success, there is a need for additional research on genes and related molecular pathways that can determine the efficacy and toxicity of lipid-lowering drugs. Several variations within genes associated with lipid metabolism, including those involved in uptake, distribution and metabolism of statins have been reported. The purpose of this study was to evaluate the effect of genetic variations in the key genes responsible for statins' metabolism and their role in personalised medicine and pharmacogenetic testing (PGx) in patients treated with such drugs. Genetic assessment for specific known SNPs within the most known genes such as *ABCG2*, *SLCO1B1*, *CYP3A4*, and *HMGCR*, appears likely to predict the efficacy of statin therapy and prevent their side effects but does not necessarily reduce the risk of cardiovascular events.

KEY MESSAGES

- Hypercholesterolaemia patients show different response to statin therapy.
- Several variations within genes associated with statin metabolism have been investigated.
- Genetic assessment for specific known SNPs within the most known genes may improve the efficacy of statins treatment and prevent their side effects.

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Introduction

In recent years, we have seen significant improvements in lipid-lowering therapy, with several new classes of drugs currently available or being tested in late-phase clinical trials. However, statins are still the most widely used lipid-lowering agents to reduce cardiovascular risk [1]. Statins are prescribed to lower serum LDL-C by controlling the rate-limiting enzyme in cholesterol synthesis *i.e.* 3-hydroxy-3-methylglutaryl coenzyme A reductase (*HMGCR*). This process can reduce the production of hepatic cholesterol, upregulate LDLR and increase LDL uptake [2]. The goal of lowering lipids is to reduce LDL-C by 100 mg/dL in high-risk patients and an optional target of less than 40 mg/dL in patients at highest risk [3–5].

Based on current evidence, European Society of Cardiology and the European Atherosclerosis Association (ECS/EAS) recommended the initiation of high-intensity statin therapy during the first two weeks of hospitalisation for the index acute coronary syndrome (ACS) [6,7]. Moreover, pre-treatment (or loading dose for patients already on a statin) with a high-intensity statin should be considered in ACS patients with planned invasive management [8]. Several clinical trials have revealed the effective role of statins in reducing cardiovascular events following lowering LDL-C levels [9,10]. Some medications reduce the effectiveness of statins by reducing bioavailability or increasing the metabolism of statins (*e.g.* rifampicin) [11]. Moreover, some clinical complications affecting

the metabolism of cholesterol, such as hypothyroidism, should be considered [12,13]. Besides these factors, several variations within genes associated with lipid metabolism such as genes involved in uptake, distribution and metabolism can exert their influence [14].

According to the previous reports, one of the side effects of statin treatment is myopathy that may result in treatment discontinuation [15]. There are several risk factors for statin-induced myopathy that are related to patients' characteristics such as age and genetics, and also drug-related transporter systems [16].

Statin therapy is limited in case of skeletal muscle toxicity which can be correlated with elevated systemic drug exposure. Up to 10% of statin-treated patients will experience muscle pain or weakness [17,18] and life-threatening rhabdomyolysis [19], which tend to occur several months to years after statin initiation.

In addition, LDL-C remains above the target still in a considerable proportion of the treated patients (>40%) [20]. Barriers to attain LDL-C goals include failure to initiate therapy, non-adherence, side effects, inappropriate drug/dose selection, and inadequate dose titration. Although several algorithms for dose selection have been introduced to minimise dose titration, they are not widely used, resulting in over 20% of patients with LDL-C still remaining above the target value [21]. Some studies have shown that statin therapy may change the course of clinical events without notable decrease in LDL-C [22,23]. In a study it has been showed significantly greater benefit from intensive statin therapy in carriers of rs20455 (Trp719Arg) than non-carriers which appears to be due to a mechanism distinct from lipid or CRP lowering [22]. This highlights the importance of pharmacogenomics and pharmacogenetics in predicting the therapeutic outcome. Additional research on genes, related molecular pathways, and their impact on lipid-lowering drugs would pave the road for more effective treatments [24]. Therefore, the purpose of this study was to evaluate the effect of genetic variation in the key genes responsible for statins metabolism (Figure 1) and their role in personalised medicine and pharmacogenetic testing (PGx) in patients treated with these drugs.

Genetic variants and statin efficacy

Although many of the new guidelines for cardiovascular treatments no longer specify lipid targets, many

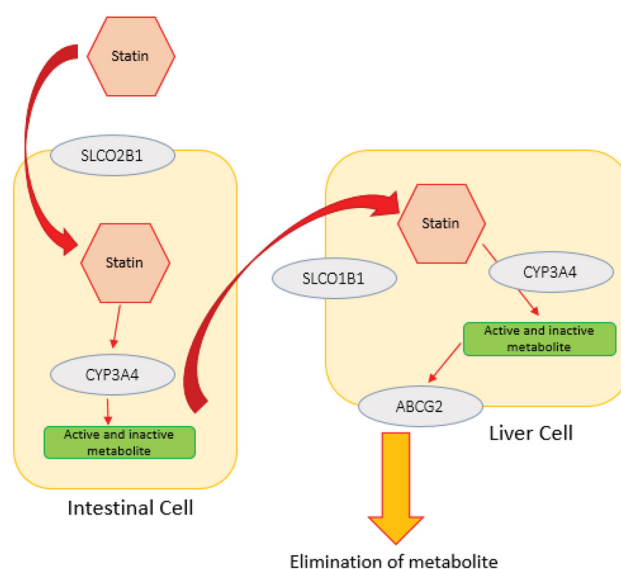


Figure 1. The simple schematic pathway for statin transporters. Statins undergo passive intestinal absorption and subsequently are taken up from the blood stream into the liver by members of solute carrier transporter family (SLCO1B1, SLCO1B3, SLCO2B1). Statins are metabolised by phase I and II enzymes and eliminated *via* efflux transporters mediated biliary excretion. Different enzymes are involved in phase I statin metabolism such as CYP3A4. Elimination of statins is carried out by members of the efflux family transporters ABCB1, ABCC2, ABCG2 or ABCB11. Statin metabolism and elimination take place primarily in the liver and to a lesser extent in the kidney.

clinicians have used lipid-lowering responses to monitor treatment efficacy and therefore optimise the statin dose. In addition to various constitutional or clinical factors (e.g. race, gender, ethnicity, and side effects) that affect statins function, genetic background can also play an important role in lipid reduction success. Increasing the dose in patients who do not show a significant decrease in lipids may also increase the risk of statin toxicity [24].

Hundreds of candidate gene studies and several genome-wide association studies (GWASs) have focussed on the influence of genetic variants on statin pharmacokinetics (e.g. drug and metabolite levels in blood, area under the time–concentration curve [AUC]) and statin pharmacodynamics (lipid lowering, incidence of adverse events, incidence of cardiovascular events). Discussing relevant clinical research, this contemporary review focuses on polymorphisms in several key genes that affect statin pharmacokinetics (e.g. transporters and metabolising enzymes), statin efficacy (e.g. drug targets and pathways), and end-organ toxicity (e.g. myopathy pathways) [17,25]. Some of key genes that affect statin pharmacokinetics

include *ABCG2*, *CYP3A4*, *HMGCR* and *SLCO1B1* are discussed in this review.

ABCG2

ATP-binding cassette G2 protein (*ABCG2*, also known as breast cancer resistance protein) is an efflux transporter which is expressed in a number of normal tissues such as brain, heart, colon, small intestine, kidney, liver, placenta, mammary gland and stem cells as well as in cancer cells [26]. *ABCG2* is a mediator of the cellular efflux of a wide range of xenobiotics including antibiotics, chemotherapeutic agent, and dietary toxins as well as endogenous compounds such as oestrogens and oestrogen conjugates. It seems that *ABCG2* protects normal cells against cytotoxic materials; however, it is also a tumour resistance inducer to several anticancer drugs [27]. *ABCG2* gene encodes the efflux transporter BCRP (Breast Cancer Resistance Protein) which is expressed on the canicular membrane of hepatocytes and in enterocytes constitutively. Rosuvastatin is actively pumped from the portal blood into the enterocytes and is thus resulting in faecal excretion of the drug. Similarly, changes in BCRP activity affects the amount of rosuvastatin circulating in the blood. It has been shown that *ABCG2*c.421C>A genetic variant leads to increased plasma concentrations of simvastatin [28] which is associated with increased risk of simvastatin induced myopathy (SIM) [29].

Absorption of *ABCG2* substrates from the gut, their entry through the blood–brain barrier and through the placenta into the foetus is limited by the *ABCG2* action. Moreover, by increasing the excretion of its substrates into the bile and urine, systemic exposure to many drugs is reduced potentially [30]. Rosuvastatin is a known substrate for *ABCG2*. One of the best-characterized sequence variations in the *ABCG2* gene is c.421C>A SNP (rs2231142), resulting in an amino acid change p. Gln141Lys. *In vitro* studies showed that the c.421A variant has been associated with reduced *ABCG2* transport activity with respect to estrone-sulfate, methotrexate, mitoxantrone, and topotecan [31]. Some studies have suggested that this SNP results in reduced expression of *ABCG2* [32,33]. Although other studies have suggested that it decreases the ATPase activity of *ABCG2* protein [30,34] while the p.Gln141Lys variant is located within the cell apart from the ATP-binding region. It has been found that in humans *in vivo*, the c.421A allele is associated with an increase in plasma concentrations of topotecan, diflomotecan, and sulfasalazine, as compared with

the c.421C allele [35,36]. The *ABCG2* c.421C>A SNP affects the pharmacokinetics of atorvastatin and rosuvastatin significantly, thus this indicates that *ABCG2* plays an important role in limiting the absorption of these statins in the gut. This effect was shown for rosuvastatin than in atorvastatin, suggesting different impact of rs2231142 on the pharmacokinetics of different statins. *ABCG2* genotyping, along with other genetic markers such as the *SLCO1B1* c.521T>C SNP, might be used to personalise selection of a statin and related dose [28].

CYP3A4

It has been known that hepatic isoenzyme *CYP3A4* is metabolising simvastatin, and to a lesser extent, atorvastatin [37]. Inhibitors or inducers of this enzyme affect the plasma concentration of these statins, then results either in an increased risk of side effects such as myopathy and rhabdomyolysis or a reduction in the efficacy of treatment [38]. The primary metabolic pathway for statins such as lovastatin, simvastatin and atorvastatin is *CYP3A4*. It has been shown that *CYP3A4* activity can be varied up to 10-fold among groups of affected individuals which may result from variations in genes encoding for these enzymes [39]. A study reported association of *CYP3A4* promoter variant (rs2740574) with higher LDL-C levels after treatment in 340 hypercholesterolaemia patients treated with atorvastatin 10 mg/day, though carriers of the missense variant (rs4986910) revealed an enhanced efficacy response and lower LDL-C levels in comparison with the wild-type allele [39]. rs2740574- the promoter variant- alters efficiency of transcription with high *CYP3A4* activity resulting in rapid drug metabolism and subsequent lower plasma concentration of atorvastatin [40]. It is reported that individuals with wild-type genotype for rs2740574 variant, had a significantly greater reduction in LDL-C as compared to the variant allele (G allele). Though, they found no association between rs4986910 variant and response to atorvastatin [41]. Moreover, another study on Indian population demonstrated no significant association between rs2740574 and lower LDL-C levels in response to atorvastatin [42]. Despite the significant pharmacokinetic interactions between inhibitors and inducers of *CYP3A4* and lovastatin/simvastatin, their clinical relevance appears to be limited, especially at lower statin doses. However, combination of statins with fibrates, mainly gemfibrozil considerably increases the potential for muscular toxicity [43].

HMGCR

As above described, statins inhibit the rate-limiting enzyme in cholesterol synthesis – namely, *HMGCR* [2]. There are wide inter-individual differences in response to statin therapy and serum lipid levels [44]. Despite the undeniable environmental impact, variations observed in serum lipid levels in different individuals are primarily described by genetic variability [45,46]. Although recent evidence suggests that *HMGCR* genotypes elucidated less than 2% of the variance in statin response, alternative splicing of *HMGCR* can explain 6 to 15% of its variance [47,48]. Alternative splicing of *HMGCR* pre-mRNA on exon 13, produces two transcripts as full-length (FL) *HMGCR* and $\Delta 13$ *HMGCR* which is related to rs3846662 [49]. Exon 13 encodes a part of the catalytic/statin-binding domain of the *HMGCR* [50,51]. It is likely that rs3846662 modifies the binding motif of heterozygous nuclear ribonucleoprotein A1 (HNRNPA1) which regulates alternative splicing of *HMGCR* [52]. According to these findings, it is suggested that an increase in the amount of $\Delta 13$ *HMGCR* mRNA in individuals carrying the rs3846662 A allele [53], results in probable lower activity in *HMGCR* [53], as well as lower levels of baseline LDL-C and reduced sensitivity and response to the statin inhibition [48,54]. A cohort of familial hypercholesterolaemia patients indicated that alternative splicing of *HMGCR* would explain 22 to 55% of the variance in statin response. A study showed that rs3846662 and the alternative splicing of *HMGCR* mRNA have a significant effect on women's response to statin therapy [55].

LDLR

The presence and type of LDLR mutations influence response to lipid-lowering therapy. Numerous randomised trials have demonstrated that therapies that lower LDL-C levels by reducing LDL particles through upregulation of the LDL receptor (LDLR) reduce the risk of cardiovascular events [56,57]. There is recent evidence that the 3'-untranslated region [3-UTR] of LDLR is required for berberine-mediated LDLC reduction through a mechanism that increases LDLR mRNA stability. Single-nucleotide polymorphisms (SNPs) in the 3-UTR have been associated with *in vivo* LDLC levels, as well as *in vitro* LDLR mRNA stability [58], and variation in this region may also influence statin-mediated lipid reduction [59]. It has been identified that some variants within the *LDLR* gene are associated with attenuated lipid-lowering response to simvastatin treatment. Response was further reduced in individuals with both LDLR and previously described *HMGCR*

haplotypes [60]. Numerous variants through the LPL pathway and current therapies that lower LDL-C levels through the LDLR pathway were also associated with similar lower CHD risk per unit lower plasma ApoB levels [61].

SLCO1B1

The *SLCO1B1* gene encodes a protein called organic anion transporting polypeptide 1B1, or *OATP1B1* which is found in liver cells. *OATP1B1* transports bilirubin, certain hormones, toxins, and drugs into the liver for removal from the body [62]. Several drugs are normally transported by the *OATP1B1* protein including statins, heart disease medications, certain antibiotics and some cancer therapy drugs [63,64]. Among statins, rosuvastatin is an inhibitor of 3-hydroxymethylglutaryl co-enzyme A reductase which inhibits 3-hydroxymethylglutaryl co-enzyme A reductase, and therefore leads to reduced production of mevalonic acid by hepatocytes. This results in reduction of total circulating levels of cholesterol and LDL-C in the blood. One of the most commonly used drugs in the treatment of hypercholesterolaemia, hypertriglyceridaemia, hyperlipidaemia, mixed dyslipidemia and homozygous familial hypercholesterolaemia is rosuvastatin [65]. Additionally, rosuvastatin and pitavastatin have been proposed as probe substrates for *OATP1B*. Prueksaritanont et al. showed relative sensitivity and selectivity to *OATP1B* inhibitors. They recommended pitavastatin over rosuvastatin as a more sensitive and selective clinical *OATP1B* probe [66].

The most comprehensively studied example is the effect of the missense variant rs4149056 in *SLCO1B1* (*SLCO1B1**5 and part of *SLCO1B1**15) that results in elevated statin plasma concentrations due to impaired hepatic clearance [67,68] and, in the case of simvastatin use, this increased exposure has convincingly been associated with increased risks of developing myopathy [69]. Based on these and other similar reports, important information on *SLCO* allele frequency with putative clinical relevance have been provided [70–73]. The pharmacogenetics of rosuvastatin has been influenced by *SLCO1B1*c.521T>C (rs4149056, p. Val174Ala) and *ABCG2*c.421C>A (rs2231142, p. Gln141Lys) genetic variants. *OATP1B1*- encoded by *SLCO1B1*- is responsible for the uptake of rosuvastatin by hepatocytes and from the intestinal lumen by enterocytes. Consequently, each polymorphism that alters *OATP1B1* activity affect plasma levels of rosuvastatin. The *SLCO1B1* c.521T>C SNP has been shown to reduce *OATP1B1* transporter activity [74] and therefore,

elevates rosuvastatin concentrations/exposure in plasma which leads to an increased risk of statin-induced myopathy [67].

Statins structure and types

Statins are made in two ways, either of fungal-derived or synthetically products. Fungal-derived statins includes lovastatin, pravastatin, and simvastatin and synthetic compounds consists of atorvastatin, cerivastatin, fluvastatin, pravastatin, pitavastatin, and rosuvastatin [75,76]. There are functional differences between natural and synthetic statins that depend on their ability to interact and inhibit HMG-CoA reductase and their hydrophobicity. Due to the structural properties of statins, synthetic forms are more likely to interact with HMG-CoA reductase. Atorvastatin and rosuvastatin are more likely to interact with hydrogen. In addition, rosuvastatin also has a polar interaction between the methane sulphonamide group and the HMG-CoA reductase enzyme. Therefore, rosuvastatin has the greatest effect on reducing HMG-CoA reductase activity by up to 50% [76,77]. Due to the polar hydroxyl group and methane sulphonamide, pravastatin and rosuvastatin are hydrophobic. Lovastatin, fluvastatin, simvastatin and atorvastatin are relatively lipophilic compounds. Lipophilic statins (except pitavastatin and cerivastatin) are less bioavailable compounds because of their first-pass effect on the liver surface [77,78]. Side effects, such as muscle toxicity, have been reported due to the penetration of lipophilic statins into the extrahepatic tissue. But hydrophilic statins are excluded from the extracellular tissue because of the need for active transport mechanisms in the liver. However, there is a balance between the favourable and side effects of lipophilic and hydrophobic statins [77].

As mentioned previously, a common nonsynonymous variant in the drug transporter *SLCO1B1* (rs4149056) has been associated with a 4-fold increase

in the risk of myopathy among patients with high dose simvastatin usage at genome-wide levels of statistical significance [69]. This finding has been widely proved in several studies [63,79,80]. Attempts to find additional common variants related to statin-related muscle injury have failed to yield replicable results [81,82]. A recent study conducted whole-exome sequencing on 88 Czech patients with mild statin-associated muscle toxicity, demonstrated an increased burden of rare variants in 24 genes [83].

Individual polymorphic forms of the same drug substance may differ in their physical properties such as chemical reactivity, solubility and dissolution rate, stability, melting and sublimation temperature, density, hardness, adsorption, hygroscopicity and refractive index. It is particularly crucial for statins, which are poorly soluble and have low bioavailability. The low total bioavailability of statins creates the need for new polymorphic forms that will increase the therapeutic effect and reduce the dose of the drug taken by the patient. Based on the available scientific reports, it can be concluded that amorphous forms of statins create the possibility of increasing the solubility and bioavailability of this group of drugs, which in turn is an opportunity to increase their effectiveness in the treatment of cardiovascular diseases [84].

Statins and personalised medicine

Personalised medicine in cardiovascular diseases has advanced rapidly, with PGx applications accessible for both researchers and clinicians. This may help selection, dosing and monitoring of drugs [85,86]. It seems that the variations in genes involved in statins metabolic pathways may influence the therapeutic effectiveness of these drugs (Table 1). Genetic assessment for specific known SNPs appears likely to improve the efficacy of statins treatment and prevent their side effects but does not necessarily predict a reduction in the risk of cardiovascular events by

Table 1. The most known genetic variants in statins pharmacogenetics reported on ClinVar/PharmKG.

Gene	rs Number	Effect	Drug	Outcome	References
<i>SLCO1B1</i>	rs4149056	c.521T>C (p.Val174Ala)	Simvastatin Rosuvastatin Pravastatin Cerivastatin	CC: higher risk of myopathy CT: intermediate risk of myopathy	[64, 68, 79, 87]
	rs4149015	c.-910G>A (upstream variant)	Pravastatin Pitavastatin	AA: decreased response AG: intermediate response	[87–89]
<i>ABCG2</i>	rs2231142	c.421C>A (p.Gln141Lys)	Rosuvastatin	GG: reduced response GT: intermediate response	[90,91]
<i>HMGCR</i>	rs17238540	g.27506T>G (Intron Variant)	Pravastatin	GG: reduced response TG: intermediate response	[92]
	rs3846662	g.23092A>G (Intron Variant)	Simvastatin Pravastatin	GG & AG: Probability of reduced response due to deletion of exon 13 of <i>HMGCR</i> gene	[53, 93]

statins [94]. In addition, PGx test can be performed as a valuable tool for clinicians to monitor the treatment process of patients with statin therapy. Catalan and LeLorier [95] showed that only 33% of patients still adhere to statin therapy after 1 year. Another study by Dorais et al. [96], showed that among the 19,727 statin-treated patients, 53.3% stopped taking the drug after 1 year.

It is likely that pharmacogenetic testing will become a routine part of clinical practice in the near future. Notably, the rapid progress in technology and increased application of NGS techniques have allowed a paradigm shift from candidate variant researches towards comprehensive analyses of genomic makeup. Personalised medicine is still in its infancy; however, there are challenges such as ethical, behavioural, methodological, technical and financial issues in providing an available service for all patients around the world based on causal variants at associated loci.

According to the results of clinical trials as well as systematic reviews and well-powered GWAS, variants in several genes such as APOE, LPA, ABCG2, SLCO1B1 have been confirmed to affect LDL-C response to statins and are likely to have a limited effect on clinical benefit. Although there are various reports of association of different SNPs affecting only clinical benefit of statin therapy, such claims mostly rely on questionable evidence. Genetic variation, without a doubt, can affect statin response; however, due to the small effect sizes of these variants, using such information in clinical decision-making should be made with caution. The consideration of interaction between gene and environment and the application of “omics” data in PGx studies will assist the reliable outcomes and new strategies of pharmacogenomics research and development.

Disclosure statement

The authors declare that they have no competing interests.

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