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Association between selected gene polymorphisms and statin metabolism, risk of ischemic stroke and cardiovascular disorders

Związek wybranych polimorfizmów genów z metabolizmem statyn, ryzykiem udaru niedokrwiennego mózgu i chorób sercowo-naczyniowych

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Summary

Statins are increasingly widely used in primary and secondary prevention of cardiovascular disorders, including ischemic stroke. The initial studies regarded mainly coronary heart disease, but recently more attention has been paid to statin use in ischemic stroke, including primary and secondary prevention as well as the acute phase treatment. Besides their main hypolipemic activity, statins have been proved to have immunomodulating properties that are called a pleiotropic effect. Drug metabolism is under genetic influence, exemplified by the single nucleotide polymorphisms (SNPs). This also applies to statins. Pharmacogenetic studies are conducted in many disorders including stroke. The aim of this study was to review selected common genetic variants in lipid or statin metabolism-related genes and indicate associations with cardiovascular disorders, especially with ischemic stroke. We present available data of SNPs in regard to the most significant and promising proteins such as cytochrome P450, ATPase superfamily, organic anion transporter family, apolipoprotein E, lipoprotein-associated phospholipase A₂, lipoprotein(a), LDLR, proprotein convertase subtilisin/kexin type 9, HMGCR, and CETP. A presentation of particular SNPs may help in future studies to aim for individual and thus more effective statin therapy in stroke patients.

Keywords: pharmacogenetics • genetic polymorphism • stroke • statins • stroke prevention • stroke pharmacogenetics

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Abbreviations: **ABC** – ATP-binding cassette; **ApoE** – apolipoprotein E; **C** – complement; **CETP** – cholesteryl ester transfer protein; **CHD** – coronary heart disease; **CVD** – cardiovascular disease; **FH** – familial hyper-

cholesterolemia; **HDL-C** – high-density lipoprotein cholesterol; **HMGCR** – HMG-CoA reductase; **HMG-CoA** – 3-hydroxy-3-methylglutaryl coenzyme A; **IMT** – intima-media thickness; **IS** – ischemic stroke; **LDLR** – low-density lipoprotein receptor; **LDL-C** – low-density lipoprotein cholesterol; **Lp(a)** – lipoprotein(a); **Lp-PLA₂** – lipoprotein-associated phospholipase A₂; **MI** – myocardial infarct; **OATP1B1** – organic anion transporter family; **PCSK9** – proprotein convertase subtilisin/kexin type 9; **RCTs** – randomized control trials; **SNP** – single nucleotide polymorphism; **TG** – triglycerides; **TGF** – transforming growth factor; **TIA** – transient ischemic attack; **t-PA** – tissue-plasminogen activator; **VLDL-C** – very low density lipoprotein-cholesterol.

INTRODUCTION

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) inhibit HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reduction to mevalonate, which leads to decreased synthesis of endogenous cholesterol. It has been demonstrated that statins additionally modify the inflammatory process by acting on the immune system (pleiotropic effect). Statins are more widely used in primary and secondary stroke prevention [52]. Statins exert their main effect on lipids, among which LDL-C (low-density lipoprotein cholesterol) is one of the most important risk factors of stroke [78].

The hypolipemic activity of statins is modified by genetic factors. There have been found several gene polymorphisms (single nucleotide polymorphism, SNP) that affect statin activity [53,79]. However, pharmacogenetic variability may also be a risk factor for adverse drug reactions [59]. In this manuscript we will mainly concentrate on potential gene polymorphisms that may play an important role in stroke primary and secondary prevention.

Ischemic stroke is a multifactorial disease and a major cause of death and disability throughout the world. Acquired risk factors (e.g. hypertension, cigarette smoking, and diabetes mellitus) account only for about 69% of the population-attributable risk. Thus, it is likely that other, as yet unidentified factors contribute to the development of stroke. Both epidemiologic and animal-based studies suggest that alterations in a variety of candidate genes, including hemostatic genes, genes controlling homocysteine metabolism, the gene that encodes angiotensin-converting enzyme, and the gene that encodes endothelial nitric oxide synthase, are important in the pathogenesis of ischemic stroke. Apparently the genetic influences are polygenic. In addition, ischemic stroke comprises many different phenotypes. According to previous studies, genetic factors seem to have different effects depending on stroke etiology [32].

The aim of this study was to review selected common genetic variants in lipid and statin metabolism-related genes and indicate associations with cerebrovascular risk factors, cardiovascular events and especially with ischemic stroke. As primary and secondary prevention of stroke may require the use of a higher dose of statins, we will present only the most important issue regarding

the side-effects and safety of such treatment. A presentation of particular SNPs may help in future studies to aim for individual and thus more effective statin therapy in stroke patients.

Figure 1 presents statin pharmacokinetics and pharmacodynamics. [106]

CYTOCHROME P450

The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. The enzyme is also known to metabolize many xenobiotics [92]. Human cytochrome P450 isoenzymes are encoded by 57 genes encoding the active forms of P450 and 58 pseudogenes without any open reading frame found. Based on the protein primary structure the cytochrome P450 isoenzymes are classed as families and superfamilies. Enzymes that belong to one family show more than 40% and 55% similarity of protein primary structure in one superfamily [87].

The cytochrome P450 isoenzyme 3A5 (CYP3A5) plays an important role in biotransformation and metabolism of certain drugs. Some of the SNPs have been associated with variations in enzyme activity. Statins are metabolized by CYP450 isoenzymes in the liver, but there are vast differences in metabolism of different statins (table 1).

The CYP3A5*3A allele was associated with lower total and LDL-C response to atorvastatin treatment in hypercholesterolemia patients of non-African ethnicity, but there was no such effect in African descent individuals. The ethnic differences are of clinical importance also in other gene SNPs [108]. On the other hand, the rs10242455, rs10264272, rs776746 polymorphisms of the CYP3A5 gene were not associated with LDL-C response to simvastatin treatment [40]. The

Table 1. Cytochrome P450 isoenzyme and statin metabolism [6,50,75,110]

Statin	P450 isoenzyme
Fluvastatin	CYP2C9
Atorvastatin	CYP3A4, CYP3A5
Rosuvastatin	CYP2C9, CYP2C19
Simvastatin	CYP3A4, CYP3A5, CYP2C*
Lovastatin	CYP3A4, CYP3A5



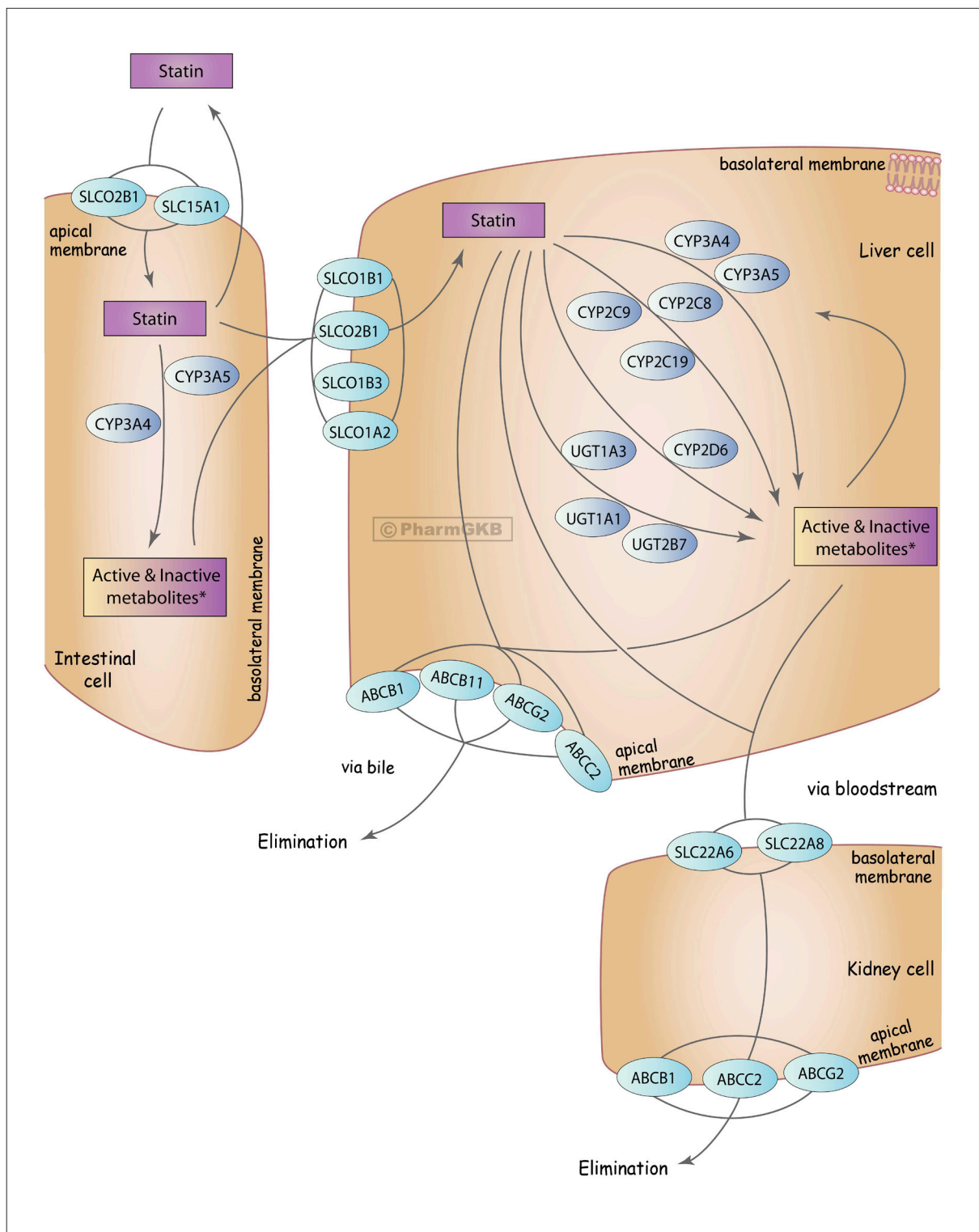


Fig. 1. Statin pathway – generalized, pharmacokinetics; permission has been given by PharmGKB and Stanford University, original source and legend available online at <https://www.pharmgkb.org/pathway/PA145011108#PGG>

SNP CYP3A4*1G of cytochrome P450 isoenzyme 3A4 (CYP3A4) increased the lipid-lowering effects of atorvastatin on the blood total cholesterol level in hyperlipidemic patients, but there was no such effect on other

lipid parameters or when simvastatin was used [34]. The lipid-lowering therapy was influenced by isoenzyme polymorphism CYP2D6 in simvastatin-treated patients with hypercholesterolemia [67].

The 1347G/A polymorphism of the *CYP4F2* gene was found to be an important risk factor for cardioembolic stroke [68]. Other results suggest that genetic variation rs1799998 (-344C/T) of the *CYP11B2* gene may contribute to the risk of ischemic stroke with a moderate effect in the Han Chinese population [98]. The *CYP4F2* gene polymorphism V433M (rs2108622) was associated with increased risk of ischemic stroke in the male Chinese Han and male Swedish populations [21,28]. The results of another study were consistent with regard to this polymorphism and to *CYP4A11* C296T polymorphism [23].

Contrary results were provided in a study showing no association between *CYP2C9*2* (rs1799853) and *CYP2C9*3* (rs1057910) polymorphisms and risk of subclinical atherosclerosis, ischemic vascular disease (including ischemic stroke) or death after ischemic heart disease [47]. The *CYP2C9*2* and *CYP2C9*3* alleles did not represent risk factors for ischemic stroke in another study [32]. No evidence of an association was also found between variation in *CYP2J2*, *CYP2C8* or *CYP2C9* and stroke [63].

There have been no eligible studies analyzing the potential effect of *CYP* gene polymorphism on statin response in stroke patients. Available data suggest such a relationship in accordance with clopidogrel use in the acute phase of stroke. The *CYP2C19* genotypes had a significant impact on clopidogrel response, prognosis of patients with stroke and risk of bleeding complications [8,46]. The role of *CYP2C19* variants was observed as a risk factor of primary endpoint (cardiovascular death, myocardial infarction or stroke) during clopidogrel treatment [65].

EFFLUX TRANSPORTERS

The membrane-associated protein encoded by the *ABCA1* gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intracellular membranes. ABC genes are divided into seven distinct subfamilies (*ABCA1*, *MDR/TAP*, *MRP*, *ALD*, *OABP*, *GCN20*, *White*). With cholesterol as its substrate, this protein functions as a cholesterol efflux pump in the cellular lipid removal pathway. Mutations in this gene have been associated with familial high-density lipoprotein cholesterol (HDL-C) deficiency [90].

The SNP of the *ABCA1* gene was associated with variation in plasma HDL-C level. The 105CT/TT genotypes were associated with higher HDL-C and lower VLDL-C (very low-density lipoprotein cholesterol) and triglycerides compared to the -105CC carriers. The R219K SNP was associated with lower triglyceride and VLDL-C levels.

The effects of SNPs C14T, R219K and C105T of the *ABCA1* gene on serum lipids were not modified by atorvastatin treatment [35]. The rs11887534 SNP of *ABCG5* was strongly associated with LDL-C response to atorvastatin [95]. The rs12003906 SNP of the *ABCA1* gene was

associated with a reduced statin effect on LDL-C [102]. The rs2002042 polymorphism of the *ABCC2* gene had a significant effect on lipid response to simvastatin treatment. No such effect was observed in rs1481012 and rs2231142 SNP of the *ABCG2* gene and rs4299376 of the *ABCG5/8* gene [40].

The rs4149264 SNP of the *ABCA1* gene and two polymorphisms of the *ABCG5* gene (rs4245786 and rs1864815) were found to modify the effectiveness of statins in reducing the risk of myocardial infarction (MI) [72]. SNP-related statin interaction effects on MI but not on stroke incidence were observed in rs194581 of the *ABCB1* gene [38]. Individuals with the *ABCB1* TT genotype of 3435C/T polymorphism had reduced platelet inhibition and are at increased risk of achieving the primary endpoint (cardiovascular death, myocardial infarction or stroke) during clopidogrel treatment, while G2677T/A and C1236T polymorphisms did not show any effect [65].

The *ABCG2* gene encodes the protein ABCG2 (BCRP – breast cancer resistance protein), whose activity is modified by SNPs [2]. The *ABCG2* gene 421C>A (Q141K, rs2231142) polymorphism may play an important role in the pharmacokinetics of rosuvastatin in healthy male subjects [112]. The same polymorphism was associated with interindividual variability of rosuvastatin concentration in other studies [18,49,113]. It was also demonstrated that its effect on statin concentration is different in particular types of statins [48]. There was detected an effect of rosuvastatin on LDL-C reduction in association with rs2231142, rs1481012 and rs2199936 of *ABCG2* gene polymorphisms [9,96]. The Val12Met SNP (rs2231137) in the *ABCG2* gene is associated with higher incidence of ischemic stroke [58]. The role of *ABCG2* gene polymorphisms in stroke prevention in relation to statin use needs further studies. This concerns especially rs2231137, which is one of the most studied ones.

UPTAKE TRANSPORTERS

The *SLCO1B1* gene encodes a liver-specific member of the organic anion transporter family (OATP1B1). The encoded protein is a transmembrane receptor that mediates the sodium-independent uptake of numerous endogenous compounds including bilirubin, 17-beta-glucuronosyl estradiol and leukotriene C4. This protein is also involved in the removal of drug compounds such as statins from the blood into the hepatocytes. Polymorphisms in the gene encoding this protein are associated with impaired transporter function [93].

The GG A388G (rs2306283) homozygotes of *SLCO1B1* gene polymorphism showed a decrease in triglycerides (TG), whereas there was an increase in TG following atorvastatin treatment in Egyptian female AA and AG carriers [83]. The authors of another study suggested possible gender-dependent effects of the rs4149056 variant within the *SLCO1B1* gene on statin treatment efficacy by means



of lipid profile change [45]. The 388A>G and 521T>C polymorphisms of the *SLCO1B1* gene were not associated with atorvastatin and simvastatin lipid-lowering effects in Chinese patients. Different effects of SNPs may be associated with ethnicity, as different allele distribution between ethnic groups was observed [31]. In the Heart Protection Study participants rs2306283 and rs12372157 were not associated with lipid response to simvastatin. On the other hand, the rs4149056 and rs11045819 polymorphisms of the *SLCO1B1* gene were confirmed to alter the lipid response to simvastatin therapy, but did not significantly reduce the risk of major vascular events [40].

The SNP *SLCO1B1**5 allele was associated with simvastatin-induced side effects [103], but there was no increased risk of myalgia among rosuvastatin users who carry the rs4363657C or the rs4149056C allele in the *SLCO1B1* gene [16]. The potential association between variants of SNP and side effects may lead to dose decrease or drug switching during simvastatin therapy, which concerns the c.521T>C polymorphism (rs4149056) of the *SLCO1B1* gene [17]. The genotyping of *SLCO1B1* polymorphisms may be useful in the future for tailoring both the statin dose and safety monitoring, especially when statins are used in combination with certain other drugs and during the first year of treatment, when the absolute risk of myopathy is greatest, in order to obtain the benefits of statin therapy more safely and effectively. Overall, more than 60% of these myopathy cases could be attributed to the rs4149056 C variant in *SLCO1B1*. The cumulative risk of myopathy among patients taking 80 mg of simvastatin daily with respect to the rs4149056 genotype was estimated. CC homozygotes had an 18% cumulative risk, with myopathy occurring primarily during the first year, whereas the cumulative risk of myopathy was only 0.6% among TT homozygotes who were taking 80 mg of simvastatin. The odds ratio for myopathy was 4.3 (95% CI, 2.5 to 7.2) per copy of the C allele and 17.4 (95% CI, 4.8 to 62.9) among CC homozygotes as compared with TT homozygotes [56]. Genotyping of that gene should be strongly considered for inclusion in clinical practice, especially in the case of patients administered high statin doses, as it has the strongest and most consistent association with the risk of myopathy.

APOLIPOPROTEIN E

Apolipoprotein E (ApoE) has been widely studied in regard to its role in lipid transport and metabolism. Apo E is polymorphic with three isoforms, ApoE2, ApoE3 and ApoE4, which translate into three alleles of the gene. Total cholesterol and LDL cholesterol were associated with ApoE isoforms [89]. The ApoE ϵ 2 allele was associated with lower LDL cholesterol and the ϵ 4 allele with higher LDL cholesterol in both Whites and African Americans [101]. There was found a significant association between ApoE polymorphisms and LDL-C levels in patients with familial hypercholesterolemia (FH). The -1131C variant of the ApoA5 gene was associated with

increased baseline TG in both patients with and without FH [43].

Neither ApoE nor ApoA5 polymorphisms showed a significant effect on the lipid responses to rosuvastatin [43]. There were detected APOE gene polymorphisms that were associated with the simvastatin effect on LDL-C reduction (rs4803750, rs2075650, rs7412, rs4420638, rs405509), and one SNP did not show such a relationship (rs8106922) [40]. rs7412 was the SNP most strongly associated with LDL-C response to atorvastatin. A weaker association was observed for SNP17 and rs429358 of the APOE gene [95]. There was found an association of LDL-C response to atorvastatin that reached genome-wide significance within the APOE region (rs445925 and rs4420638, which are proxies for the ϵ 2 and ϵ 4 variants, respectively, in the APOE gene) [22]. The APOE gene polymorphism rs7412 had an impact on rosuvastatin-induced LDL-C change [9]. The rs7412 (ϵ 3 allele) SNP of the APOE gene is associated with a reduced statin effect on LDL-C [102].

APOE polymorphism may be a risk determinant of atherosclerosis [111]. The ApoE ϵ 2 and ϵ 4 alleles were associated with carotid IMT (intima-media thickness) measures in both racial groups, but after adjusting for lipid parameters only the ϵ 4 allele was associated with carotid IMT measures in African Americans. These allele did not predict incident coronary heart disease in either racial group [101]. In another study no statistically significant differences of carotid intima thickness among subgroups divided according to their ApoE genotype were found [41]. Association between ApoE ϵ 2, ϵ 3, ϵ 4 isoforms and IMT was found with segment-specific distribution pattern [89]. A meta-analysis published in 2004 confirmed the ϵ 4 polymorphism of the ApoE gene as a significant risk factor for coronary heart disease (CHD) [85]. A meta-analysis published in 2013 that assessed the relationship between the Chinese population and CHD revealed an association between the ApoE ϵ 4 allele and increased risk of CHD [109]. There is also a paper analyzing the potential role of this SNP regarding stroke. The authors collected case-control studies of cerebral infarction patients in the Chinese population and found that the APOE ϵ 4 allele is associated with an increased risk of developing cerebral infarction [105]. A meta-analysis of 26 eligible studies on ischemic stroke (IS) patients showed that ϵ 4 allele-containing genotypes were significantly associated with IS (odds ratio [OR], 1.11; 95% CI, 1.01 to 1.22). Associations appeared stronger with ϵ 4+ genotypes for large artery compared with other IS subtypes and for Asian compared with white populations. However, no association was found between ϵ 4+ genotypes and IS when only larger studies (> 200 cases) or studies without control selection bias were analyzed [86].

The protective effect of statins on the risk of myocardial infarction and stroke was independent of apoE genotype [60].

LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A₂

Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) is a proinflammatory enzyme bound to plasma lipoproteins in the circulation (approx. 70–80% to LDL-C and the remainder to HDL-C and VLDL-C), and it is a risk factor as strong as LDL-C [13,107]. A rare loss of function mutation in the gene encoding Lp-PLA₂ (*PLA2G7*) was associated with lower risk of developing CHD among South Koreans. Genome-wide analysis of baseline Lp-PLA₂ activity identified 2 genome-wide significant loci at *APOE* (rs7412) and *MS4A4E* (rs600550) and for genome-wide analysis of Lp-PLA₂ mass identified 2 loci, *CETP* (rs3764261) and *GCKR* (rs1260326), that met genome-wide significance thresholds. In analysis of change in Lp-PLA₂ activity after 12 months of statin therapy, there were identified 2 novel genome-wide loci, *ABCG2* (rs2199936) and *LPA* (rs10455872), with differential effects on lowering Lp-PLA₂ activity in those randomly allocated to rosuvastatin versus placebo. The effect of *ABCG2* and *LPA* gene polymorphisms possibly showed up because of their impact on statin-induced LDL-C lowering [13,94].

Lp-PLA₂ activity is significantly lowered with high-dose statin therapy and is associated with an increased risk of CV events independent of C-reactive protein and LDL cholesterol levels [70]. Epidemiological studies have associated both higher concentrations of Lp-PLA₂ and elevated Lp-PLA₂ enzyme activity with greater risk of developing atherosclerosis and cardiovascular disease (CVD), independent of the risk associated with circulating lipid levels. An increase in circulating Lp-PLA₂ may transiently indicate symptomatic transformation of the carotid atherosclerotic plaque [69]. Elevated Lp-PLA₂ mRNA expression seems to be a potential biomarker for predicting an unfavorable outcome in patients with acute ischemic stroke [97]. Significant changes in Lp-PLA₂ concentrations occur early after stroke onset. Lp-PLA₂ mass may add relevant information regarding early arterial recanalization in intravenous t-PA-treated stroke patients [20]. Both Lp-PLA₂ activity and mass were associated with stroke recurrence in patients with a transient ischemic attack (TIA), which may be helpful in the early evaluation of such patients [19]. The Lp-PLA₂ mass and activity measured 3 months after stroke are associated with recurrent vascular events [64].

LPA

The *LPA* gene encodes lipoprotein(a) (Lp(a)), which is an LDL-like molecule. Lp(a) inhibits activation of transforming growth factor (TGF) and contributes to the growth of arterial atherosclerotic lesions, inhibits plasminogen binding to the surfaces of endothelial cells, decreases the activity of fibrin-dependent tissue-type plasminogen activator, and may act as a proinflammatory mediator that augments lesion formation in atherosclerotic plaques. The *LPA* SNP rs10455872 has been associated with an LDL-C lowering response to statins in several

randomized control trials (RCTs) and is a known CHD marker. The effect of simvastatin on LDL-C was modified depending on the genotype of the *LPA* gene polymorphisms rs3798220 and rs10455872 [40]. There was found an association of LDL-C response to atorvastatin that reached genome-wide significance at rs10455872 within the *LPA* gene [22]. The *LPA* gene polymorphism rs10455872 had an impact on rosuvastatin-induced LDL-C change [9].

Many observations have pointed out that Lp(a) levels may be a risk factor for cardiovascular diseases. The rs10455872, rs6919346, rs10455872, rs6919346, and rs3123629 SNPs of the *LPA* gene were significant predictors of carotid artery disease defined as > 80% internal carotid artery stenosis [80]. In a meta-analysis, modest associations of Lp(a) concentration with risk of CHD and stroke were observed [27,61]. Lp(a) levels are largely determined by alleles at the hypervariable gene locus [81]. On the other hand, it was demonstrated that the rs3798220 polymorphism of the *LPA* gene is not useful for predicting statin-induced cardiovascular risk reduction [4]. The *LPA* gene variants rs6415084 and rs3798220 have no relationship with subsequent cardiovascular events (including ischemic stroke) after percutaneous coronary intervention (PCI) in Chinese Han CHD patients [55]. The *LPA* gene variants rs10455872 and rs3798220 were associated with earlier onset of CHD, risk of ischemic stroke and with IMT, but not with the IS of cardioembolic subtype [37]. In a prospective analysis there was not found any significant association between rs10455872 polymorphism in the *LPA* gene and CVD incidence in type 2 diabetes patients [76]. rs3798220 and rs10455872 of the *LPA* gene were associated with the risk of CHD and peripheral vascular disease but not with stroke [39].

In a meta-analysis published in 2013 it was shown that individuals with the G allele of rs10455872 polymorphism have a higher risk of CHD than the majority of the population even after treatment with statins [25]. Similar studies regarding ischemic stroke are desirable to identify patients at higher risk of cerebrovascular episodes. Such information may help in the use of more personalized and efficacious treatment.

LDLR

The LDL receptor (LDLR) plays a crucial role in the catabolism of LDL-C, and upregulation of its activity is associated with statin LDL-C lowering therapy [73].

Six SNPs of the *LDLR* gene, i.e. G44243A, G44332A, C44506G, G44695A, C44857T and A44964G, clustered in three haplotypes, were associated with a lower LDL-C level in Caucasians, but not in African Americans [66]. The A370T polymorphism of the *LDLR* gene was not associated with plasma lipid levels [99].

An association was found between simvastatin LDL-C lowering effect and rs5930 of the *LDLR* gene [40]. Similar



results were obtained in relation to the effect of atorvastatin with rs10455872, rs1433099, rs5925 and rs688 [22,95]. Such an effect was not observed by other authors concerning polymorphisms rs6511720, rs688, rs1433099, rs8102273, rs11668477, rs2228671, rs1799898, rs2569538 [40]. Negative results were also obtained for an association between lipid-lowering effect of simvastatin and polymorphisms rs14548, rs1433099, rs7254521, rs5742911, rs2738467 of the *LDLR* gene, but significant correlations were observed when these SNPs were analyzed in certain haplotypes [62]. Similarly, SNP rs6511720 of the *LDLR* gene did not have an influence on lipid-lowering therapy with statins [104]. For the *LDLR* gene SNPs C44857T (rs1433099) and A44964G (rs2738466) there were noted significant associations with baseline LDL-C and triglyceride levels and a modest association of C44857T with LDL-C lowering by pravastatin in men [10].

The rs6511720 polymorphism mutational status in the *LDLR* gene was associated with the extent of subclinical computed tomography coronary artery atherosclerosis in patients with FH [88]. The *LDLR* gene SNPs C44857T and A44964G showed significant associations with incident CHD and CVD, especially in men on pravastatin [10]. The rs031163 polymorphism of the *LDLR* gene was significantly associated with both MI and stroke [38]. There was found no significant difference in the genetic frequency of rs688 and rs5925 of the *LDLR* gene between the healthy control group and ischemic stroke subjects. However, when analyzing the association between the haplotypes related to rs688 and rs5925 and cerebral ischemic stroke, there was evidence suggesting that genetic polymorphisms of the *LDLR* gene are associated with cerebral infarction [54]. The A370T polymorphism of the *LDLR* gene was not associated with CHD or stroke [99]. There have been no studies analyzing the potential effect of statins in acute phase, primary and secondary prevention of stroke in relation to *LDLR* gene polymorphisms.

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9

Proprotein convertase subtilisin/kexin type 9 (*PCSK9*), a serine protease, has recently gained a lot of attention because of its major role in regulation of plasma LDL-C levels. High levels of *PCSK9* lead to high plasma levels of LDL-C, whereas low levels of *PCSK9* lead to low LDL-C levels. The Y142X, C679X and R46L polymorphisms were associated with a lower LDL-C level [15]. The E670G polymorphism of the *PCSK9* gene modulates plasma LDL-C levels [42]. Rosuvastatin increased plasma concentration of *PCSK9* in proportion to the magnitude of LDL-C reduction. The rs11591147 SNP of the *PCSK9* gene was strongly associated with LDL-C response to atorvastatin [95]. The R46L (rs11591147) SNP at the *PCSK9* locus was associated with significantly lower LDL-C in response to pravastatin, whilst the E670G SNP did not show such an effect [74]. Two polymorphisms, rs11206510 and rs6235, of the *PCSK9* gene did not modify the effect of atorvastatin and simvastatin on lipids [104]. The R46L SNP did

not alter the magnitude of LDL-C reduction associated with rosuvastatin use in a randomized trial [5].

The E670G polymorphism of the *PCSK9* gene can be used as a predictor of large-vessel atherosclerosis stroke and is associated with severity of intracranial atherosclerosis in the circle of Willis and in its branches in autopsy studies [1]. On the other hand, the E670G variant was shown to be an independent determinant of plasma LDL-C levels and the severity of coronary atherosclerosis [10]. The I474V and E670G variants in the *PCSK9* gene were not associated with either lipid levels or CHD risk in healthy men [82]. In a meta-analysis the authors confirmed the effect of *PCSK9* R46L polymorphism on reduction in LDL-C and CHD. Moreover, the reduction in risk of CHD was larger than predicted by the observed reduction in LDL-C alone [7]. Neither R46L nor E670G SNP of the *PCSK9* gene reduced the CHD risk in an elderly population with a high prevalence of cardiovascular disease [74]. The Y142X, C679X and R46L polymorphisms were associated with decreased risk of CHD and lower mean IMT. Depending on the mutation, the impact of genotype was an 88% reduction in the risk of CHD in black subjects (47% in whites) [15]. It was also suggested that polymorphisms rs630431 and rs560892 of the *PCSK9* gene may have interactions with postmenopausal hormone therapy and risk of stroke [44].

Two polymorphisms of the *PCSK9* gene (rs10888896 and rs505151 (E670G)) were found to modify the effectiveness of statins in reducing the risk of MI [72].

HMGCR

HMG-CoA reductase (*HMGCR*) is an enzyme involved in cholesterol synthesis and is the target of statin therapy [11]. The -911C>A polymorphism (rs33761740) of the *HMGCR* gene was associated with TC levels in CHD patients [3]. The rs10474433, rs17671591 and rs6453131 SNPs were strongly associated with LDL-C response to atorvastatin [95]. The *HMGCR* gene rs3846662 GG genotype was documented to be a significant determinant for higher LDL-C level in the basal state and possibly in response to atorvastatin [14]. Other results indicated a strong association of rs12916 variants of the *HMGCR* gene with the reduction of LDL-C after statin treatment [12]. On the other hand, SNPs rs3846662 and rs6453139 were not associated with the effect of simvastatin on LDL-C [40]. Similarly, rs12654264 of the *HMGCR* gene did not have an influence on lipid-lowering therapy with statins [104]. Other authors did not find any relationships between the 18 T >G (rs17238540) *HMGCR* gene polymorphism, baseline lipid values and statin-induced LDL-C lowering response [10]. The rs17238540 SNP in the *HMGCR* gene may be associated with a worse response to statin therapy in terms of TC and TG lowering [24].

An association between the rs17238540 SNP and the stroke risk was observed [30]. The rs17238540 SNP of the *HMGCR* gene was not significantly associated with the

risk of MI, stroke and interactions between statins and these disorders [38]. Similarly, the 18 T >G *HMGCR* gene polymorphism was not associated with incident CHD and CVD [10].

CETP

The protein encoded by this gene is found in plasma (cholesteryl ester transfer protein), where it is involved in the transfer of cholesteryl ester from HDL-C to other lipoproteins [91]. Its role remains a subject of debate and may be antiatherogenic or proatherogenic [51].

There are results suggesting that -629A/C *CETP* gene polymorphism influences baseline HDL-C and CETP

levels, though patients with CC genotype appeared to benefit more from atorvastatin therapy with reduction in LDL-C and LP(a) levels [33]. The effect of simvastatin on LDL-C was influenced by rs3764261 and rs7499892 polymorphisms of the *CETP* gene, but such an effect was not observed in rs708272 and rs5882 [40].

Genetic variants in the *CETP* gene (rs708272 and rs12149545) were not associated with recurrent MI or recurrent revascularization, but the rs708272 SNP was associated with increased mortality in atherosclerotic subjects [100]. The absence of the Taq1B2 allele was associated with increased risk of CHD [57]. In the Whitehall II study, both rs247616 and rs5883T/rs9930761C (analyzed as associated polymorphisms) were independently

Table 2. SNPs of selected genes and their effect on ischemic stroke risk

SNP and gene	Effect	Group	Odds Ratio (95% CI)
1347G/A, <i>CYP4F2</i> gene	risk factor for cardioembolic stroke	507 IS patients	1.25 (1.054-1.504) [72]
rs1799998 (-344C/T), <i>CYP11B2</i> gene	risk factor of IS	558 IS patients	1.57 (1.14-2.16) [98]
V433M (rs2108622), <i>CYP4F2</i> gene	1. Higher IS incidence in males	302 IS patients	1.746 (not available) [20]
	2. Risk factor of stroke	122 IS patients	1.69 (1.10-2.60) [27]
	3. Higher incidence of stroke	558 IS patients	1.38 (1.15-1.65) [22]
C296T, <i>CYP4A11</i> gene	higher incidence of stroke	558 IS patients	1.50 (1.17-1.93) [22]
<i>CYP2C19</i> gene variants	increased risk of primary endpoint (cardiovascular death, myocardial infarction or stroke) during clopidogrel treatment,	2932 patients with acute coronary syndromes	1.77 (1.11–2.80) [69]
3435C/T, <i>ABCB1</i> gene	increased risk of primary endpoint (cardiovascular death, myocardial infarction or stroke) during clopidogrel treatment	2932 patients with acute coronary syndromes	2.01 (1.30–3.11) [69]
Val12Met, <i>ABCG2</i> gene	increased risk of stroke in follow up	cohort of 4522 participants	white population: 1.46 (1.05-2.03), black population: 3.59 (1.11-11.6) [62]
<i>APOE</i> gene ε4 allele	1. Risk factor of IS 2. Increased risk of stroke	2737 IS patients	2.82 (2.16-3.67) [105]
		meta-analysis of 5961 IS patients	1.11 (1.01-1.22) [90]
Combined rs3798220(C) and rs10455872(G), <i>LPA</i> gene	increased risk of stroke	9396 IS patients	1.10 (1.02-1.18) [35]
rs031163, <i>LDLR</i> gene	increased risk of stroke	368 IS patients	1.20 (1.02-1.41) [37]
rs688 of <i>LDLR</i> gene	increased risk of stroke	815 IS patients	1.32 (1.00-1.73) [56]
rs5925 of <i>LDLR</i> gene	increased risk of stroke	815 IS patients	1.48 (0.81-2.68) [56]
rs630431, <i>PSCK9</i> gene	increased risk of stroke	263 IS patients	1.994 (1.362-2.919) [47]
rs560892, <i>PSCK9</i> gene	increased risk of stroke	263 IS patients	2.019 (1.373-2.967) [47]
rs17238540, <i>HMGCR</i> gene	increased risk of stroke	cohort of 23,011 participants	1.44 (1.05-1.97) [29]
rs5883T/rs9930761C, <i>CETP</i> gene	increased risk for an event in males (MI, stroke, death)	cohort of 4745 participants	2.36 (1.29-4) [75]
rs12720922, <i>CETP</i> gene	increased risk of stroke	cohort of 3898 participants	1.24 (1.03-1.51) [25]
rs9939224, <i>CETP</i> gene	increased risk of stroke	cohort of 3898 participants	1.26 (1.05-1.51) [25]
rs5883, <i>CETP</i> gene	increased risk of stroke	368 IS patients	3.06 (1.22-7.70) [37]
rs008764, <i>CEP</i> gene	increased risk of stroke	368 IS patients	1.25 (1.04-1.50) [37]



associated with increased HDL-C levels in males. In an independent multiethnic cohort of hypertensive subjects with CHD, rs5883T/rs9930761C alone was significantly associated with increased incidence of MI, stroke, and all-cause mortality in males. These variants did not reach significance in females in either study. Similar to earlier results linking low CETP activity with poor outcomes in males, our results suggest genetic, sex-dependent CETP splicing effects on cardiovascular risk by a mechanism independent of circulating HDL-C levels [71]. The minor alleles of two *CETP* gene SNPs (rs12720922 and rs9939224) were associated with a higher ischemic stroke risk [26]. On the other hand, some data suggest that the Taq1 B2 allelic variant of the *CETP* gene may be associated with lower occurrence of ischemic stroke [77]. Another study showed that Taq1 B polymorphism of the *CETP* gene is not associated with ischemic stroke [29].

The interaction between statins and cardiovascular risk and *CETP* gene polymorphisms was assessed in relation to rs008764 and rs5883. The latter was associated with the strongest increase in risk of stroke among statin users [38].

CONCLUSIONS

Hypolipemic and preventive effects of statins are under the influence of genetic factors such as SNPs of certain genes. In this review we presented potential genetic variants that can be more precisely analyzed in future studies. Genotyping may determine whether statins should be used, or used in a lower or higher

dose, taking into consideration expected beneficial and side-effects.

Pharmacogenetics and its application in medicine to individualize drug therapy has been previously shown to be clinically and economically beneficial. In the cost-effectiveness model of using the genetic test results for two *LPA* gene variants (rs3798220 and rs10455872) to identify patients likely to benefit from aspirin use in the primary prevention of cardiovascular disease, it was suggested that this could be cost-effective [84].

While conventional pharmacogenetic studies have considered single gene effects, a genetic score of nine LDL- and HDL-associated SNPs, previously shown to predict cardiovascular disease, may be related to fluvastatin-induced lipid change in women with asymptomatic plaque in the carotid artery. These genes for LDL-C score were *APOB* (rs693), *APOE* (rs4420638), *HMGCR* (rs12654264), *LDLR* (rs1529729), and *PCSK9* (rs11591147), and for HDL-C score they were *ABCA1* (rs3890182), *CETP* (rs1800775), *LIPC* (rs1800588) and *LPL* (rs328) [36]. The lipid-lowering response to simvastatin was reduced in individuals with combined *LDLR* and *HMGCR* gene haplotypes [62].

The reviewed gene polymorphisms affecting the lipid profile, statin metabolism and cerebrovascular risk factors in relation to pharmacokinetic and pharmacodynamic profiles of statins need further research, aiming for application in personalized, safer and more efficacious therapy.

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