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Cholesteryl Ester Transfer Protein and ATP-Binding Cassette Transporter A1 Genotype Alter the Atorvastatin and Simvastatin Efficacy: Time for Genotype-Guided Therapy?

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Abstract

We compared the efficacy of atorvastatin with simvastatin according to cholesteryl ester transfer protein (CETP) and adenosine triphosphate-binding cassette transporter A1 (*ABCA1*) genes. Patients treated with atorvastatin (n = 254) or simvastatin (n = 332) were genotyped for CETP (TaqIB and I405V) and ABCA1 (R219K) genetic variants. For genotype *B1B2*, atorvastatin compared with simvastatin treatment resulted in a greater decrease in total cholesterol (35.4% vs 31.6%, *P* = .035) and a lower increase in high-density lipoprotein cholesterol (2% vs 8%, *P* = .05). For genotype *B2B2*, atorvastatin compared with simvastatin treatment resulted in a lower decrease in low-density lipoprotein cholesterol (31.85 vs 42%, *P* = .029). For genotypes RR and KK, atorvastatin compared with simvastatin treatment resulted in a greater decrease of triglycerides (27% vs 17% and 35% vs 15%, respectively; *P* = .02 for all comparisons). The TaqIB and R219K (opposite to I405V) gene polymorphisms seem to modify the response to lipid-lowering therapy with simvastatin or atorvastatin treatment.

Keywords

atorvastatin, simvastatin, cholesteryl ester transfer protein (*CETP*) gene, ATP-binding cassette transporter A1 (*ABCA1*) gene

Introduction

Cholesteryl ester transfer protein (CETP) mediates the transfer of cholesteryl esters from high-density lipoprotein (HDL) particles to apolipoprotein (apo) B-containing lipoproteins in exchange for triglycerides (TGs).[1] Several CETP gene polymorphisms have been identified. More frequently studied are I405V with II, IV, and VV genotypes and TaqIB with B1B1, B1B2, and B2B2 genotypes.[2-4] The adenosine triphosphate (ATP)-binding cassette transporter A1 (ABCA1) acts as a vehicle for cellular cholesterol which, after crossing the cell membrane, binds to acceptor molecules such as apo A.[5] ABCA1 influences the initial steps in HDL particle formation and in reverse cholesterol transport. Several ABCA1 gene polymorphisms were identified, including rs2230806 (R219K) which codes RR, RK, and KK genotypes.

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the first-line drug treatment for elevated plasma low-density lipoprotein cholesterol (LDL-C) concentration. However, there is considerable variation in statin-induced LDL-C reduction (25%-60%).[6] Similar variations have been reported for statin effects on TGs (from −10% to −50%) and HDL cholesterol (HDL-C, from −1% to +15%). Environmental and genetic factors may contribute to this variability.

The considerable individual and societal costs of drug treatment dictate a need for effective interventions. Two

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Table 1. Patient Characteristics at Baseline[a]

Age, years	57 ± 13
Gender, male/female, %	69/31
BMI, kg/m^2	27 ± 4
TC, mg/dL	281 ± 56
TG, mg/dL	176 ± 124
HDL-C, mg/dL	49 ± 14
LDL-C, mg/dL	194 ± 57
CAD, yes/no, %	43/57
Hypertension, yes/no, %	50/50
DM, yes/no, %	23/77
Smoking, yes/no/ex, %	29/40/31

Abbreviations: BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CAD, coronary artery disease; DM, diabetes mellitus.
[a] For TC, HDL and LDL, to convert from milligrams per deciliter to millimoles per liter divide by 38.8. For TG, to convert from milligrams per deciliter to millimoles per liter divided by 88.6.

strategies for achieving improved treatment outcomes are to optimize pharmacotherapies and to personalize treatment options. Thus, the study was conducted to provide initial experience with the genotype-guided statins. In line with our previous work,[7,8] we assessed the effects of 2 commonly used statins (atorvastatin and simvastatin) on the lipid profile (total cholesterol [TC], LDL-C, TGs, and HDL-C), according to CETP gene polymorphisms. In the present study, we evaluate a larger population, also assess the *ABCA1* gene, and compare the effect of these 2 statins (ie, atorvastatin and simvastatin).

Participants and Methods

Participants

A total of 586 Greek unrelated participants with hypercholesterolemia (406 men and 180 women), aged 57.2 (±13.1) years were genotyped. Additional inclusion criteria included a stable medication that were unlikely to interfere with lipid profile (patients with coronary heart disease were on cardioselective β-blockers and aspirin, whereas patients with hypertension were on angiotensin-converting enzyme inhibitors) and routine lifestyle for at least 4 weeks prior to study screening. Individuals with a history of renal or thyroid disease and uncontrolled diabetes mellitus were excluded from the study. Patients were assigned to atorvastatin or simvastatin treatment for at least 6 months. The dose of atorvastatin (10-40 mg/d) or simvastatin (10-40 mg/d) was adjusted, according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[9] treatment goal for LDL-C based on risk category (LDL-C <130, <100, or <70 mg/dL; <3.4, <2.6 or <1.8 mmol/L). All participants were started on atorvastatin or simvastatin as the only lipid-lowering drug. To reduce the possibility of potential bias, the choice of drugs was left to the 6 prescribing physicians. Our institutional review board approved the study.

DNA Analysis and Determination of Blood Lipids and Glucose

The CETP (TaqIB, I405V) polymorphisms were detected using polymerase chain reaction (PCR) and restricted fragment length polymorphism (RFLP) analysis as described previously.[10,11] The R219K of ABCA1 gene polymorphism was detected using PCR and RFLPs. The PCR was performed using *Taq* polymerase KAPATaq. For R219K polymorphism, AAAGACTTCAAGGACCCAGCTT and cctcacattccgaaagcatta oligonucleotide primers were used.[12] The PCR was subjected to 95°C for 5 minutes, 30 cycles of 95°C for 30 seconds, 55°C for 30 seconds, 72°C for 30 seconds, and final extension to 72°C for 7 minutes, producing a fragment of 309 bp. This fragment was subsequently cleaved by *Eco*NI, creating fragments for R allele 309 bp and for K allele 184 bp and 125 bp, which were subjected to electrophoresis on an agarose gel 3% and visualized with ethidium bromide.

Levels of TC, TG, and HDL-C were measured using enzymatic colorimetric methods, on a Roche Integra Biochemical analyzer, with commercially available kits (Roche Diagnostics Gmbh, Hannheim, Germany). Levels of LDL-C were calculated using the Friedewald formula in participants with TG levels <400 mg/dL.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as frequencies. Student *t* tests for independent and paired variables were used in order to evaluate the differences in continuous variables between different groups and between baseline and after treatment, respectively. Differences in TC, TGs, HDL-C, and LDL-C before and after atorvastatin or simvastatin treatment were also described as percentage difference, based on the following rule: percentage difference = [(variable after − variable before)/variable before] × 100. All tests were 2-sided at a significance level of $P < .05$. Data were analyzed using STATA statistical software (version 9.0, Stata Corporation, College Station, Texas).

The number of patients needed to obtain 90% power for reaching significance in a 2-sided test at the 5% level was determined for each of the main outcome variables (percentage difference in TC), assuming that the true relative reductions in the 2 drug treatment groups (atorvastatin vs simvastatin group) differed by 5%. This resulted in a requirement of 99 patients in each treatment group.

Results

All participants were genotyped and treated with simvastatin (n = 332) or atorvastatin (n = 254). Levels of TC, LDL-C, and TG were significantly decreased after simvastatin (−31.4%, −39.3%, and −18.2%, respectively; $P < .001$ for all comparisons) and atorvastatin (−33.8%, −39.5%, and −24.0%, respectively; $P < .001$ for all comparisons) administration. Concentration of HDL-C increased by 5.4% ($P = .01$) in the

Table 2. Baseline Lipid Profile of the Simvastatin and Atorvastatin Groups Based on TaqIB, I405V, and ABCA1 Genotypes

		TC (mg/dL), (mean ± SD)	TG (mg/dL), Median (IQR)	HDL-C (mg/dL), Median (IQR)	LDL-C (mg/dL), Median (IQR)
Simvastatin					
TaqIB	B1B1	275 ± 43	143 (92)	46 (16)	186 (48)
	B1B2	287 ± 65	136 (85)	48 (18)	195 (58)
	B2B2	267 ± 44	150 (88)	47 (14)	173 (50)
	P value	.116	.448	.550	.193
I405V	II	283 ± 61	150 (95)	45 (15)	186 (60)
	IV	274 ± 44	133 (79)	49 (20)	191 (51)
	VV	284 ± 65	127 (86)	47 (14)	199 (79)
	P value	.469	.182	.301	.988
ABCA1	RR	285 ± 64	131 (82)	48 (15)	191 (59)
	RK	272 ± 44	149 (92)	46 (17)	185 (54)
	KK	278 ± 38	139 (124)	46 (21)	197 (40)
	P value	.596	.129	.650	.150
Atorvastatin					
TaqIB	B1B1	283 ± 57	159 (125)	41 (14)	189 (61)
	B1B2	294 ± 53	142 (102)	48 (20)	201 (73)
	B2B2	283 ± 50	129 (82)	50 (15)	201 (75)
	P value	.396	.393	**.002**	.556
	II	284 ± 55	153 (90)	43 (16)	200 (70)
I405V	IV	295 ± 54	142 (110)	49 (20)	195 (78)
	VV	286 ± 47	120 (84)	48 (16)	201 (94)
	P value	.280	.222	**.006**	.802
ABCA1	RR	300 ± 53	145 (86)	48 (19)	212 (69)
	RK	282 ± 56	142 (102)	47 (21)	187 (64)
	KK	279 ± 31	154 (143)	44 (14)	199 (63)
	P value	.261	.633	.504	**.031**

Abbreviations: TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

simvastatin group and by 3.0% ($P = .95$) in the atorvastatin group.

Genotype and Allele Frequencies in the Studied Groups

In the whole cohort, genotype frequency of I405V and TaqIB polymorphisms was 43.8% for II, 44.9% for IV, and 11.3% for VV; and 33.5% for B1B1, 49.7% for B1B2, and 16.8% for B2B2, respectively. In the whole cohort, the genotype frequency of ABCA1 (R219K) polymorphism was 47% for RR, 43.8% for RK, and 9.2% for KK.

Patient Characteristics

Baseline patient characteristics are shown in Tables 1 and 2.

Genotype Influence on TC and TGs According to Both Regimens

CETP (TaqIB). In individuals with genotype B1B2 (49.7% of all individuals), atorvastatin treatment resulted in a greater decrease (percentage difference) of TC and a lower increase of HDL-C than in individuals with the same genotype treated with simvastatin (Table 3). In individuals with genotype B2B2, atorvastatin treatment resulted in a lower decrease (percentage difference) of LDL-C than in individuals with the same genotype treated with simvastatin (Table 3).

ABCA1 (R219K). In individuals with genotypes RR and KK (56% of all individuals), atorvastatin treatment resulted in a greater decrease (percentage difference) of TGs than in individuals with the same genotype treated with simvastatin (Table 3).

Genotypes Without Percentage Difference Between the 2 Regimens. In genotypes B1B1, II, IV, VV, and RK, no percentage differences were found between the 2 regimens.

The HDL-C Concentrations Before and After Therapy by Statin and Genotype in Patients With Baseline HDL-C <40 mg/dL. Simvastatin increased HDL-C levels in all genotypes except VV, while atorvastatin increased HDL-C levels only in few genotypes (Figure 1A, B, and C).

Discussion

Gene frequencies for TaqIB, I405V, and R219K polymorphisms in our cohort were similar to those reported in other caucasians[13,14] and dyslipidemic populations.[15,16]

In previous studies, we evaluated the efficacy of atorvastatin[8] and simvastatin[7] according to CETP polymorphisms and found that the effectiveness in lipid lowering may be influenced by CETP polymorphism. In the present study, we assessed more patients (273 additional individuals, 121 in the atorvastatin and 152 in the simvastatin group), evaluated 1 more polymorphism, namely ABCA1 (K219R), and compared the percentage differences in altering lipid profile by those 2 commonly used statins. We aimed to find the most suitable

Table 3. Atorvastatin Versus Simvastatin Efficacy (% Difference) by TaqIB, I405V, and R219K Genotypes

Gene	Genotype	Lipids	Atorvastatin, % difference	Simvastatin, % difference	*P*
TaqIB					
	B1B1				
		TC	−33 ± 16	−31 ± 11	.566
		TG	−17 ± 35	−20 ± 30	.556
		HDL-C	+6 ± 28	+4 ± 24	.504
		LDL-C	−39 ± 18	−40 ± 15	.769
	B1B2				
		TC	−35 ± 12	−32 ± 15	**.035**
		TG	−28 ± 32	−20 ± 33	.063
		HDL-C	+2 ± 25	+8 ± 21	.050
		LDL-C	−43 ± 14	−38 ± 23	.103
	B2B2				
		TC	−31 ± 13	−32 ± 12	.661
		TG	−23 ± 36	−12 ± 30	.156
		HDL-C	+0.1 ± 26	+2 ± 17	.702
		LDL-C	−32 ± 16	−42 ± 18	**.029**
I405V					
	II				
		TC	−35 ± 14	−32 ± 12	.060
		TG	−25 ± 30	−22 ± 33	.540
		HDL-C	+5 ± 25	+5 ± 20	.825
		LDL-C	−41 ± 17	−39 ± 16	.291
	IV				
		TC	−32 ± 13	−31 ± 14	.537
		TG	−23 ± 38	−16 ± 31	.232
		HDL-C	+3 ± 25	+5 ± 23	.532
		LDL-C	−38 ± 15	−39 ± 23	.752
	VV				
		TC	−34 ± 16	−32 ± 12	.767
		TG	−26 ± 25	−15 ± 20	.080
		HDL-C	−4 ± 33	+5 ± 22	.248
		LDL-C	−39 ± 13	−43 ± 17	.477
R219K					
	RR				
		TC	−33 ± 14	−30 ± 13	.088
		TG	−27 ± 29	−17 ± 31	**.020**
		HDL-C	+1 ± 22	+6 ± 20	.093
		LDL-C	−39 ± 17	−40 ± 18	.847
	RK				
		TC	−35 ± 11	−34 ± 12	.583
		TG	−20 ± 38	−22 ± 28	.793
		HDL-C	+1 ± 27	+2 ± 20	.864
		LDL-C	−40 ± 15	−39 ± 22	.767
	KK				
		TC	−36 ± 12	−30 ± 14	.179
		TG	−35 ± 19	−15 ± 37	**.019**
		HDL-C	+17 ± 36	+13 ± 31	.746
		LDL-C	−46 ± 16	−40 ± 18	.414

Abbreviations: TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

treatment (genotype-guided therapy) to achieve NCEP-ATP-III targets.[9]

Genome-wide association studies offer a more wide-ranging approach for identifying genetic loci associated with statin response.[17] Barber et al[17] reported that rs4420638, located in apolipoprotein (APO) C1 and near APOE, was associated with changes in LDL-C. Hoenig et al[18] found that ABCB1 influences atorvastatin efficacy. Wei et al[19] reported that the CYP7A1 204A and ABCG8 1199A alleles appeared to interact with lipid-lowering response to atorvastatin. Li et al[20] compared simvastatin versus atorvastatin efficacy, according to CYP3AP1*3 variant allele in Chinese patients with hyperlipidemia. They reported that the percentage reduction in LDL-C level was greater in the CYP3AP1*3/*3 carriers than in the CYP3AP1*1 carriers in simvastatin group but only for women. Voora et al[21] showed that

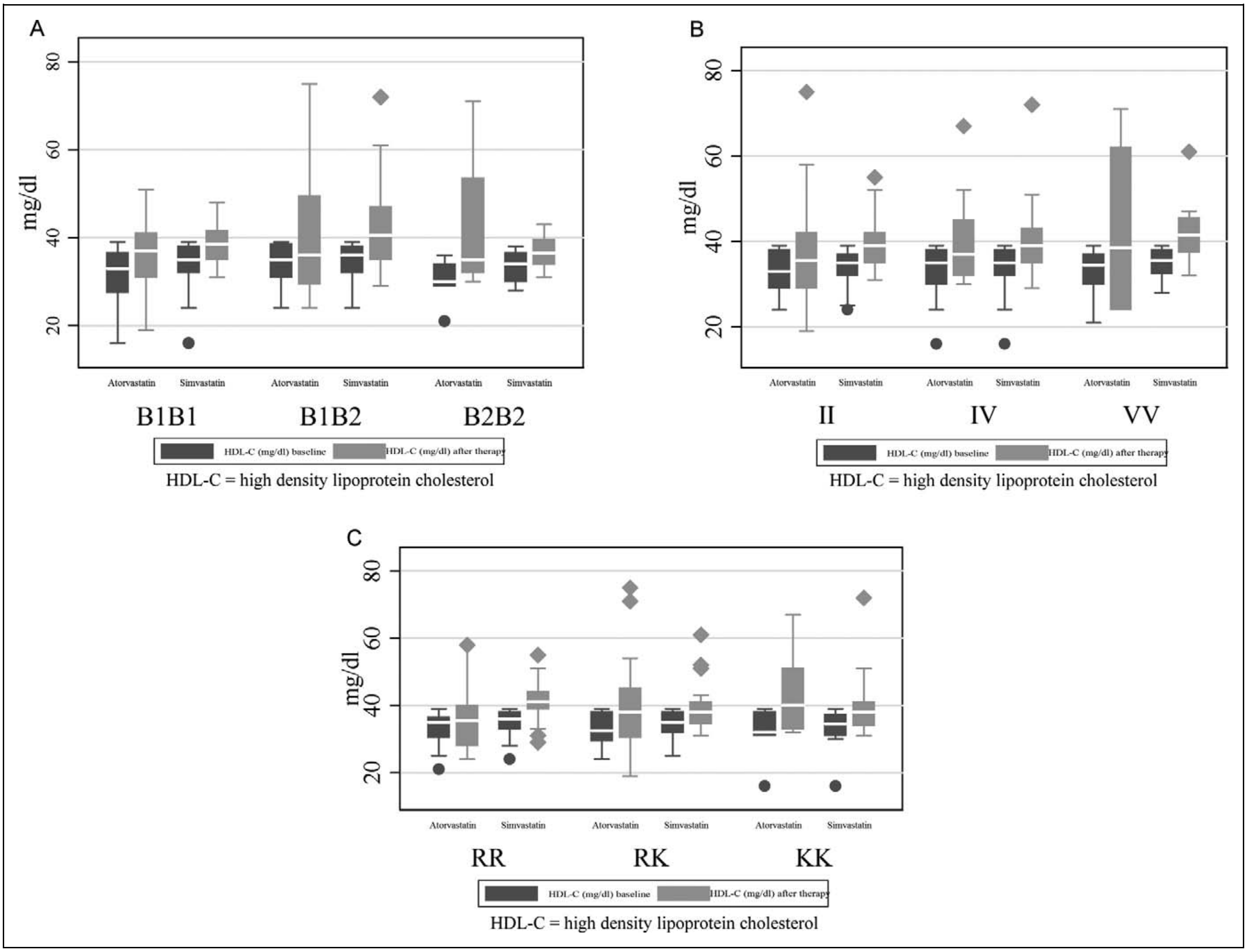

Figure 1. A, HDL-C concentrations before and after statin therapy according to CETP TaqIB genotypes in patients with baseline HDL-C <40 mg/dL. B, HDL-C concentrations before and after statin therapy according to CETP I405V genotypes in patients with baseline HDL-C <40 mg/dL. C, HDL-C concentrations before and after statin therapy according to ABCA1 R219K genotypes in patients with baseline HDL-C <40 mg/dL. HDL-C indicates high-density lipoprotein cholesterol.

patients with the minor allele ABCA1 rs12003906 had a lower LDL-C reduction with low doses of statins and that maximal statin doses improved, though may not overcome the difference in LDL-C reduction seen in carriers of the minor allele of ABCA1 rs12003906 and the ε3 allele of *APOE* gene. Although they studied different polymorphisms, this agrees with our concept that the response to lipid-lowering drug therapy is affected by gene polymorphisms.

In the present study, individuals with B1B2 genotype (approximately 50% of the study population) treated with atorvastatin had a 11% greater decrease in TC compared with individuals with the same genotype treated with simvastatin. Furthermore, individuals with RR and KK genotypes (56% of the study population) treated with atorvastatin had a greater decrease in TGs (37% and 57%, respectively) than individuals with the same genotype treated with simvastatin. Moreover, a very noticeable difference in response to the 2 regimens was observed for LDL-C in B2B2 genotypes (16.8% of the study population); simvastatin had a greater decrease compared with atorvastatin (42% vs 32%, respectively).

On the other hand, in patients with baseline HDL-C <40 mg/dL, simvastatin was effective in genotypes B1B1, B1B2, B2B2, II, IV, RR, RK, and KK, while atorvastatin was effective only in genotypes B1B1, B1B2, II, IV, and RK in terms of significantly increasing HDL-C.

Several molecular mechanisms link CETP and ABCA1 gene variants and response to simvastatin and atorvastatin treatment. First, statin treatment may be related to plasma CETP concentrations and CETP concentration is partially dependent on CETP polymorphisms. Simvastatin and atorvastatin reduce CETP concentrations.[22] Second, both statins affect postprandial TG levels which are influenced by CETP and ABCA1 genotypes.[22,23] This statin effect on postprandial TGs concentration is also achieved by limiting the production of hepatic very-low-density lipoprotein particles and by enhancing the clearance and fractional catabolic rate of circulating TG-rich lipoproteins.[24] However, other factors also influence the response to statins.

In order to define drug response, the pretreatment lipid profile is very important. In our study population, patients with genotypes showing differences (B1B2, RR, and KK) had a similar pretreatment lipid profile in both regimens, and the response to statins was not influenced by pretreatment values. Furthermore, we incorporated the percentage difference [(variable after − variable before)/variable before] × 100 for more accurate results.

A limitation of this study is the lack of randomization and the relatively small number of patients. However, treatment choice was left to the 6 prescribing physicians. The different power of the 2 statins is another issue. However, it is notable that for some genotypes the potency of the statin was reversed.

To our knowledge, this is the first study to compare the lipid-lowering effect of the 2 most prescribed statins in accordance with gene polymorphisms.

Declaration of Conflicting Interests

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