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The Cholesteryl Ester Transfer Protein (CETP) TaqIB and I405V Gene Polymorphisms and Statin Treatment

Bousoula Eleni[1]*, Kolovou Vana[1,2], Boutsikou Maria[1], Tapola Anastasia[1], Perrea Despoina[3] and Kolovou Genovefa[1]

[1]*Cardiology Department, Onassis Cardiac Surgery Center, Athens, Greece*
[2]*Molecular Immunology Laboratory, Onassis Cardiac Surgery Center, Athens, Greece*
[3]*Department of Experimental Surgery and Surgical Research, University of Athens, Athens, Greece*

Abstract

Background: Cholesterol Ester Transfer Protein (CETP) is a plasma protein that facilitates the transport of cholesteryl esters and triglycerides between the lipoproteins. It is composed mainly at the liver and it collects triglycerides from chylomicrons and VLDL and exchanges them for cholesteryl esters from HDL. By this mean, very dense LDL molecules are being formed. The latter are very atherogenetic factors.

The gene encoding CETP is located on the long (q) arm of chromosome 16 at position 21. It has been found that at least two polymorphisms in this gene, TaqIB (with B1B1, B1B2 and B2B2 genotypes) and I405V (with II, IV and VV genotypes), have been associated with different response to statin treatment.

Aim: The aim of this study was to investigate a probable correlation of the aforementioned CETP gene polymorphisms with better or worse response to two specific statins: simvastatin and atorvastatin.

Methods: The DNA of 78 subjects, 53 men (67.9%) and 25 women (32.1%) of mean age 57 ± 20 years with dyslipidemia, was analyzed for the different genotypes of the CETP gene polymorphisms TaqIB and I405V. To all these patients' simvastatin and atorvastatin were administered as lipid lower agents and they had a lipid profil test four times during the study period. Namely, before the beginning of the therapy, two months after taking the first statin (either simvastatin or atorvastatin), two months after they quitted therapy and last time two months after restarting the lipid lower therapy with the other statin.

Results: Both statins administered to patients succeeded to reduce significantly total cholesterol, triglycerides and LDL-C levels and simultaneously to augment significantly HDL-C levels. These changes have been observed in all patients independently of their genotype of the two studied CETP gene polymorphisms.

No significant differences were demonstrated in total cholesterol, triglycerides, and HDL-C and LDL-C levels before and after simvastatin and atorvastatin therapy across Taq1B and I405V genotypes. Moreover, the effect of age and gender on lipid levels, independently of which statin was used or the genotype was not significant.

Conclusion: The initial hypothesis of our study, that there is a probable correlation between different genotypes of TaqIB and I405V CETP gene polymorphisms and response to treatment with simvastatin and atorvastatin was not confirmed.

Keywords: CETP gene polymorphisms; TaqIB polymorphism; I405V polymorphism; Simvastatin; Atorvastatin

Introduction

Dyslipidemia is one of the classical major risk factors for the development of Cardiovascular Disease (CVD) [1], which is the leading cause of death in industrialized countries. Statins are the first-line drugs for dyslipidemia treatment and consequently they play a crucial role in the prevention and treatment of CVD. They are competitive inhibitors of HMG CoA reductase, which is an enzyme with a significant role in the cholesterol synthesis.

The decrease in Cardiovascular (CV) events in dyslipidemic patients reflects mainly the decrease in LDL-C, which is achieved with statins [2]. This association applies to individuals (women as well as men) without CVD as well as to patients with established disease. Indeed, the results of epidemiological studies as well as trials with angiographic or clinical endpoints confirm that the reduction of LDL-C must be of prime concern in the prevention of CVD [3].

Statin therapy is generally associated with a LDL-C lowering up to 55% [4] and a reduction of Cardiovascular (CV) events by 20–30% [5].

Statins are generally well tolerated medications. Their main side effects are related to the muscular system (including reversible myositis and rhabdomyolysis) and the liver (hepatotoxicity).

Despite the effectiveness of statins, clinical response to them differs significantly among individuals. For example, there is considerable variation in the reduction of plasma LDL-C concentration (-25% to -60%) in response to statin treatment. This is commonly due to extraneous influences. Poor compliance as manifested by erratic consumption or discontinuation of the drug is probably the most significant factor [6]. In addition, nutritional behavior and co-

***Corresponding author:** Bousoula Eleni, Cardiology Department, Onassis Cardiac Surgery Center, 356 Sygrou Avenue, 176 74 Athens, Greece, Tel: +30 6974924180; E-mail: elena_b11@hotmail.com

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administration with other drugs that intervene in their metabolism by inhibiting or inducing P450 cytochrome, play a determinant role.

For example, when statins are given together with medications, which induce cytochrome P450, they are highly metabolized and their ability to lower LDL-C is reduced. The opposite effect is observed with their co-administration of with inhibitors of cytochrome P450. In this case, the levels of statins and their effectiveness augment but the same does the probability of their side effects [7].

Also, important for the efficacy of statins is the time of their administration. With the exception of rosuvastatin and atorvastatin, all the other statins are more effective when they are being taken in the evening, reflecting the diurnal rhythm of HMG-CoA reductase activity [8].

Nevertheless, even if the influence of external factors is minimized, significant inter-individual variations in response to statins are being observed. These variations are due to intrinsic or genetically determined factors [9] as many pharmacogenetic studies have shown [10,11].

More than 40 genes have been studied for the possibility some mutations to be responsible for the reduced response of their carriers to statin treatment. For this reason, polymorphisms of genes, which participate in the synthesis, in the absorption and in the transfer of cholesterol have been studied [12].

The gene that encodes CETP and mostly its TaqIB polymorphism has been studied in many pharmacogenetic studies. At the beginning, the B2B2 genotype was correlated with lower CETP plasma levels [13], higher HDL-C levels and lower risk for Coronary Artery Disease (CAD) compared to B1B1 genotype [14-16]. However, individuals with B1B1 genotype under statin treatment showed a slower progress of CAD in comparison with B2B2 genotype carriers [17].

Boekholdt et al. [18] in their meta-analysis, confirmed the correlation between TaqIB polymorphism and HDL-C and the risk for CAD, but they did not show any significant interaction between this polymorphism and pravastatin treatment.

Moreover, the results of REGRESS (Regression Growth Evaluation Statin Study), which is the first study where a possible pharmacogenetic interaction between CETP polymorphisms and statin treatment is mentioned [19], showed significantly higher 10-year mortality in male patients under statins, who were carriers of B2 allele compared to those with B1B1 genotype [20].

It is then obvious, that we have a "paradox" with B2 allele. Despite finding that individuals with B2B2 genotype, who do not receiving statins, have lower risk for developing CAD, statin treatment is more useful in patients with B1B1 genotype, refuting the initial advantage of B2 allele in relation to CAD [11].

In summary, pharmacogenetic studies investigate genetically inherited polymorphisms, which could influence the response to medical treatment. A combined analysis of many of these studies is more possible to provide significant findings for clinical practice. This can allow clinicians in the future choosing, for every patient the most appropriate medication according to his genetic substrate.

Methods

Study population

DNA of 78 individuals, 53 men (67.9%) and 25 women (32.1%) of Greek origin and with no family ties with one another, was analyzed for the presence of common variants of TaqIB and I405V polymorphisms of CETP gene. The study group consisted of patients of mean age 57 ± 20 years with dyslipidemia, with no history of known coronary artery disease, diabetes mellitus or thyroid function disorders.

To each of these patients' two different statins: simvastatin and atorvastatin were given They were given with at least two months free of medication interval between them. The dosage of statins was defined accordingly to guidelines of the National Cholesterol Education Programme Adult Treatment Panel III. The two-month interval between the two treatments ensured that lipids levels returned every time to their values without hypolipidemic drugs. Moreover, in order to avoid any interaction, patients during the study received no other hypolipidemic drug of other categories.

Lipids levels of every patient were measured four times during the study period: before the beginning of the treatment, at least two months after taking the first statin, two months after quitting statin and finally two months after taking the second statin.

Informed consent was obtained from all subjects and the protocol was approved by the Onassis Cardiac Surgery Center Ethics Committee.

DNA analysis

The CETP gene is found in humans at the chromosome 16q21. Its TaqIB (genotypes B1B1, B1B2, B2B2) in intron 1, and I405V (genotypes II, IV, VV) in exon 14, polymorphisms were detected using Polymerase Chain Reaction (PCR) and Restricted Fragment Length Polymorphism Analysis (RFLP) [21]. The PCR was performed using Taq polymerase.

For the TaqIB polymorphism the oligonucleotide primers which were used were: sense primer 5'-CACTAGCCCAGAGAGGGAGTGCC-3' and antisense primer 5'-CTGAGCCCAGCCGCACACTAAC-3'giving a fragment of 535 bp [22]. PCR conditions were initial denaturation at 95°C for 5 min, 30 cycles of 95°C for 30 s, 65°C for 30 s and 72°C for 30 s and a final extension at 72°C for 7 min. The PCR fragment was subsequently cleaved by TaqIB polymerase (New England Biolabs, Frankfurt, Germany) at 37°C, creating two fragments of 174 bp and of 361 bp.

For the I405V polymorphism the oligonucleotide primers which were used were: sense primer 5'-TATTTTTTTCACGGATGGGCA-3' and antisense primer 5'-TTGACTGCAGGAAGCTCTGGC-3'giving a fragment of 142 bp [23]. PCR conditions were initial denaturation at 95°C for 5 min, 60°C for 1 min, 1 cycle of 72°C for 1 min, 35 cycles of 95°C for 30 s, 60°C for 30 s and 72°C for 30 s and a final extension at 72°C for 5 min. The PCR fragment was subsequently cleaved by MspI enzyme (New England Biolabs, Frankfurt, Germany) at 37°C, creating two fragments of 121 bp and of 21 bp.

All the fragments were separated on 4% agarose gel and visualized with ethidium bromide.

Statistical analysis

All data except for baseline triglycerides, followed normal distribution (Kolmogorov-Smirnov test). Non-normally distributed continuous variables are shown as median (IQR), while normally distributed ones are presented as mean ± SD. All categorical variables are presented as relative (percentage) frequencies.

The Kruskal-Wallis H statistic or One Way Anova, where appropriate, were used to compare the continuous variables among the 3 genotype groups, while the Mann-Whitney U test or the Student's T-Test, where appropriate, was used to compare the continuous variables between the 2 groups of carriers.

The effect of different demographic factors (gender, age, and medical history) as well as different genotypes on the alterations of total cholesterol, triglyceride, and HDL and LDL levels after treatment with simvastatin/atorvastatin was examined. New variables representing the % differences in total cholesterol, TGs, HDL-C and LDL-C before and after simvastatin/atorvastatin treatment were constructed. They were described as % difference and they were computed as following: % difference=[(variable after-variable before)/variable before] × 100.

Mixed linear models were used to examine whether the effect of treatment with simvastatin and atorvastatin was different according the different genotypes.

All tests were 2-sided at a significance level of $p < 0.05$. Data were analyzed using SPSS™ (Version 20.0, Chicago IL, USA).

Results

Total cholesterol, TG and LDL-C were significantly decreased (by 29.9%, 24.9%, and 35.7%, respectively) after simvastatin therapy ($p<0.001$ in each case). HDL-C levels increased after simvastatin therapy (8.7%) ($p<0.001$) (Figures 1-8; Tables 1-13).

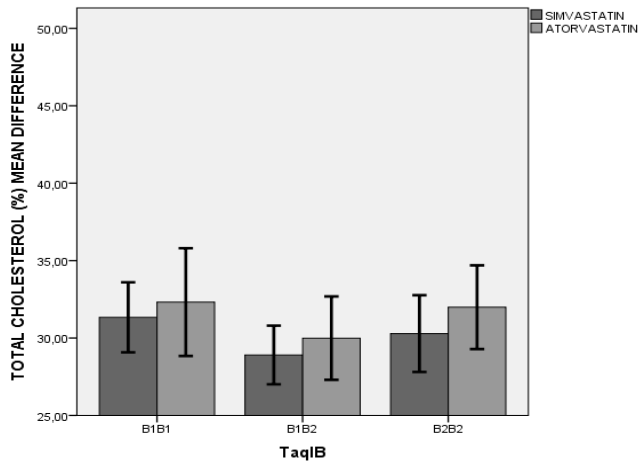

Figure 1: Total cholesterol after treatment with simvastatin and atorvastatin on TaqIB (B1B1, B1B2, and B2B2).

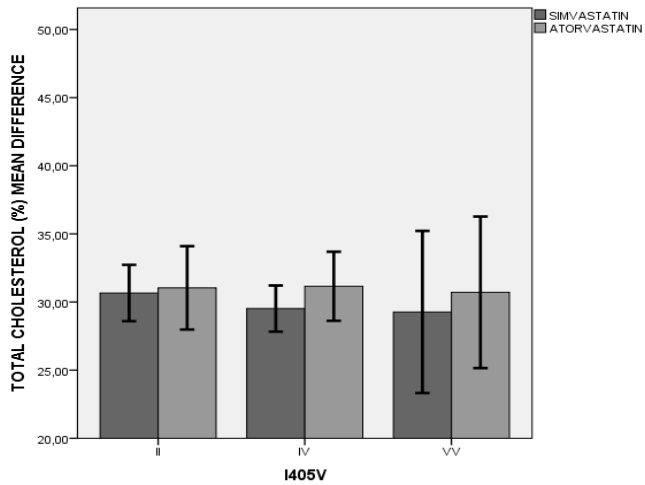

Figure 2: Treatment of cholesterol with simvastatin and atorvastatin with 1405V (II, IV, VV).

Total cholesterol, TG and LDL-C were significantly decreased (by 31.1%, 25.4%, and 39.2%, respectively) after atorvastatin therapy ($p<0.001$ in each case). HDL-C levels increased after atorvastatin therapy (8.5%) ($p<0.001$).

No significant differences were demonstrated in total cholesterol, triglycerides, HDL-C and LDL-C levels before and after simvastatin and atorvastatin therapy across Taq1B and I405V genotypes.

No significant differences were demonstrated in total cholesterol, triglycerides, HDL-C and LDL-C levels before and after simvastatin and atorvastatin therapy independently of the presence of B1, B2, I, V alleles.

Total cholesterol levels, TG, HDL-C and LDL-C were significantly decreased after simvastatin or atorvastatin therapy as described above. The % difference in lipid levels was not affected by the genotype, the statin therapy as well as whether simvastatin or atorvastatin was the first therapy. The effect of age or gender on lipid levels was not significant.

Discussion

Interventional studies with statins in the general population have shown that for every 1% reduction in LDL-C levels, there is a respective 1% decrease in the Cardiovascular (CV) events [24]. It is then absolutely clear how important is the effort for the best response

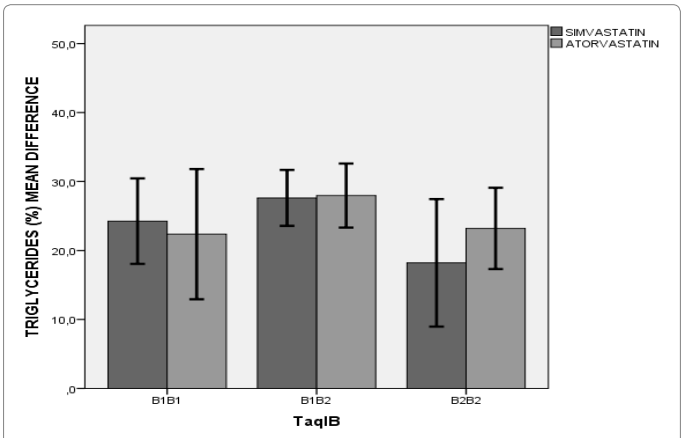

Figure 3: Treatment of triglycerides with simvastatin and atorvastatin on TaqIB (B1B1, B1B2, and B2B2).

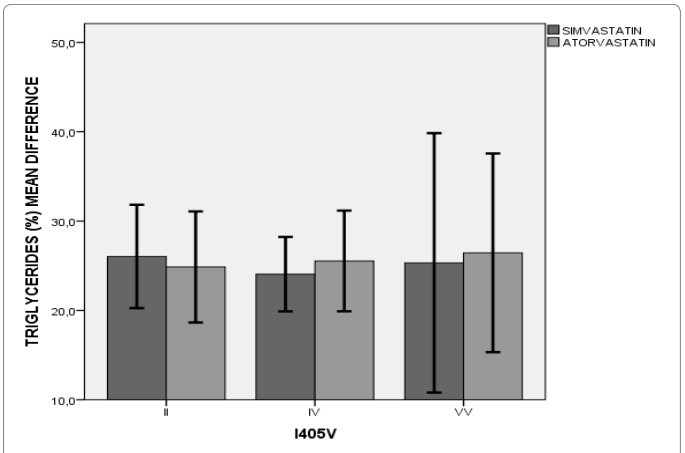

Figure 4: Treatment of triglycerides with simvastatin and atorvastatin with 1405V on B1 and B@.

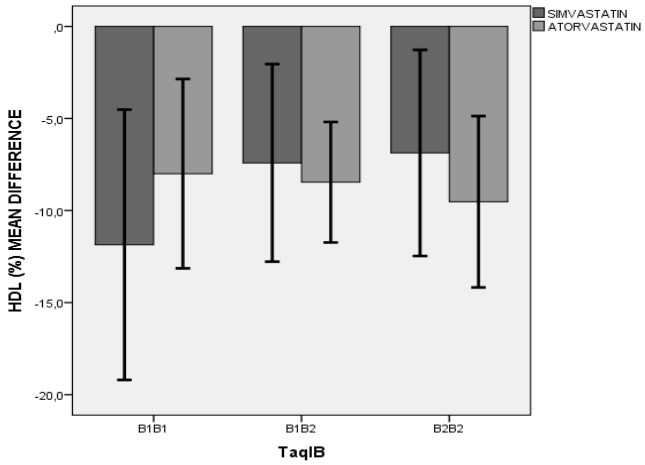

Figure 5: HDL treatment with simvastatin and atorvastatin on TaqIB (B1B1, B1B2, and B2B2).

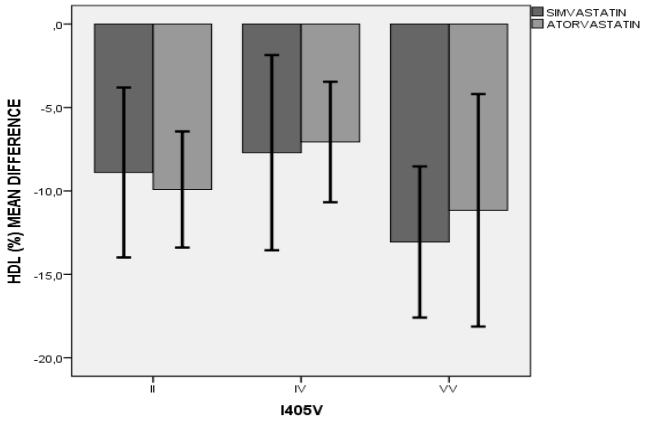

Figure 6: Treatment of HDL with simvastatin and atorvastatin with 1405V (II, IV, VV).

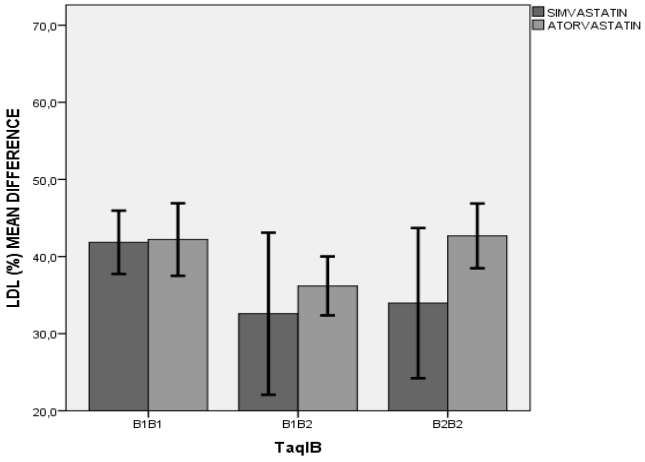

Figure 7: Treatment of LDL with simvastatin and atorvastatin on TaqIB (B1B1, B1B2, and B2B2).

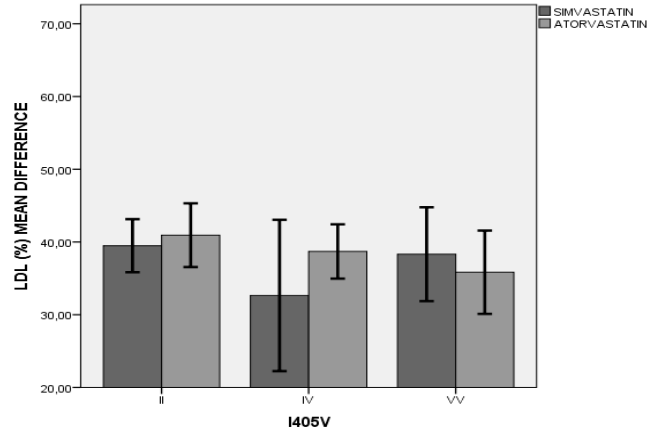

Figure 8: Treatment of LDL with simvastatin and atorvastatin on 1405V (II, IV, VV).

Variable	Mean ± SD/Median (range)
Age (years)	57 ± 20
N (%)	
Gender	
Male	53(67.9)
Female	25(32.1)
History of Coronary Heart Disease	
Yes	0
No	78

Table 1: Demographic data (all cases).

Variable	Pro Simvastatin therapy Mean ± SD/Median (range)	Pro Atorvastatin therapy Mean ± SD/Median (range)
Total Cholesterol (mg/dl)	258.4 ± 31.4	256.6 ± 28.7
Triglycerides (mg/dl)	143 (425.0-59.0)	142.5 (390.0-60.0)
HDL (mg/dl)	42 (153.0-27.0)	42.0 (95.0-26.0)
LDL (mg/dl)	179.4 ± 32.5	178.0 ± 23.3

Table 2: Baseline lipid data pre simvastatin/atorvastatin therapy (all cases).

Variable	Pro Simvastatin therapy Mean ± SD/Median (range)	Pro Atorvastatin therapy Mean ± SD/Median (range)
Total Cholesterol (mg/dl)	181.4 ± 27.5	176.4 ± 24.6
Triglycerides (mg/dl)	106.0 (246.0-40.0)	101.5 (255.0-51.0)
HDL(mg/dl)	46.0 (95.0-30.0)	46 (83.0-29.0)
LDL (mg/dl)	112.4 ± 29.0	105.5 (169.0-45.0)

Table 3: Lipid data pre simvastatin/atorvastatin therapy.

TaqIB N (%)		I405V N (%)	
B1B1	24(30.8)	II	28(35.9)
B1B2	40(51.3)	IV	42(53.8)
B2B2	14(17.9)	VV	8(10.3)

Table 4: Genotype frequencies in the whole cohort.

TaqIB (%)		I405V (%)	
B1	56.4	**I**	62.8
B2	43.6	**V**	37.2

Table 5: Allele frequencies in the whole cohort.

		TC (mg/dl) (Mean ± SD)	TG (mg/dl) Median (Range)	HDL-C (mg/dl) Median (Range)	LDL-C (mg/dl) (Mean ± SD)
Taq1B	B1B1	253.8 ± 40.2	126.0 (425.0-69.0)	41.5 (68.2-27.0)	180.3 ± 31.0
	B1B2	258.6 ± 26.3	159.0 (390.0-59.0)	41.5 (153.0-28.0)	176.9 ± 34.0
	B2B2	265.6 ± 28.7	166.0 (202.0-67.0)	42.5 (60.0-35.0)	184.4 ± 32.5
	P value	0.542	0.66	0.997	0.754
I405V	II	256.2 ± 38.4	138.0 (425.0-69.0)	41.0 (68.2-32.0)	181.7 ± 31.0
	IV	259.6 ± 27.0	158.0 (390.0-59.0)	43.5 (153.0-28.0)	177.1 ± 35.1
	VV	259.3 ± 29.4	127.5 (306.0-110.0)	38.0 (78.0-27.0)	182.5 ± 26.0
	P value	0.905	0.268	0.773	0.811

Table 6: Pre simvastatin therapy lipid profile of the study cohort based on TaqIB and I405V genotypes (all cases).

		TC (mg/dl) (Mean ± SD)	TG (mg/dl) (Mean ± SD)	HDL-C (mg/dl) (Mean ± SD)	LDL-C (mg/dl) (Mean ± SD)
Taq1B	B1B1	174.4 ± 30.3	98.0 (240.0-40.0)	46.0 (90.0-30.0)	105.7 ± 28.2
	B1B2	184.2 ± 26.9	109.0 (246.0-55.0)	46.0 (95.0-30.0)	113.3 ± 26.1
	B2B2	185.2 ± 23.6	117.5 (221.0-67.0)	45.0 (57.0-35.0)	121.2 ± 36.9
	P value	0.333	0.079	0.951	0.274
I405V	II	177.4 ± 27.2	106.0 (220.0-40.0)	45.0 (70.0-38.0)	110.4 ± 26.8
	IV	183.5 ± 27.2	106.0 (246.0-57.0)	46.5 (95.0-30.0)	113.5 ± 31.3
	VV	184.1 ± 32.0	102.0 (140.0-70.0)	44.0 (85.0-30.0)	113.5 ± 26.7
	P value	0.644	0.252	0.980	0.908

Table 7: Lipid Profile of the Study Cohort post simvastatin therapy Based on TaqIB, I405V and ABCA1 Genotypes

		TC (mg/dl) (Mean ± SD)	TG (mg/dl) Median(Range)	HDL-C (mg/dl) Median(Range)	LDL-C (mg/dl) (Mean ± SD)
Taq1B	B1B1	250.0 ± 32.1	131.0 (310.0-60.0)	44.0 (67.0-26.0)	176.8 ± 23.4
	B1B2	259.9 ± 26.7	152.0 (390.0-68.0)	41.0 (95.0-29.0)	177.1 ± 23.5
	B2B2	258.4 ± 28.1	141.0 (187.0-90.0)	42.0 (68.0-37.0)	182.8 ± 23.6
P value		0.396	0.157	0.737	0.706
I405V	II	250.9 ± 31.1	137.5 (310.0-60.0)	42.0 (67.0-31.0)	176.8 ± 24.6
	IV	259.2 ± 25.9	155.0 (390.0-68.0)	43.0 (95.0-29.0)	178.9 ± 23.9
	VV	262.6 ± 34.4	130.0 (250.0-90.0)	37.5 (80.0-26.0)	177.3 ± 16.0
	P value	0.414	0.267	0.721	0.927

Table 8: Pre atorvastatin therapy lipid profile of the study cohort based on TaqIB and I405V genotypes (all cases).

		TC (mg/dl) (Mean ± SD)	TG (mg/dl) (Mean ± SD)	HDL-C (mg/dl) (Mean ± SD)	LDL-C (mg/dl) (Mean ± SD)
Taq1B	B1B1	168.8 ± 27.5	97.5 (108.0-51.0)	46.0 (68.0-32.0)	102.6 ± 25.7
	B1B2	181.3 ± 23.7	105.5 (255.0-56.0)	45.0 (83.0-29.0)	112.2 ± 21.7
	B2B2	175.4 ± 19.5	104.5 (165.0-68.0)	46.5 (64.0-42.0)	104.9 ± 19.9
	P value	0.146	0.329	0.814	0.234
I405V	II	172.6 ± 25.7	100.0 (172.0-52.0)	47.0 (68.0-36.0)	104.8 ± 25.7
	IV	177.9 ± 24.1	107.5 (255.0-51.0)	45.0 (76.0-29.0)	108.9 ± 22.0
	VV	181.5 ± 24.7	100.0 (132.0-82.0)	41.5 (83.0-32.0)	113.9 ± 17.2
	P value	0.569	0.321	0.512	0.566

Table 9: Lipid profile of the study cohort post atorvastatin therapy based on TaqIB, I405V and ABCA1 genotypes.

		TC (mg/dl) (Mean ± SD)	TG (mg/dl) Median (Range)	HDL-C (mg/dl) Median (Range)	LDL-C (mg/dl) (Mean ± SD)
Taq1B	B1	256.8 ± 32.0	141.5 (425.0-59.0)	41.5 (153.0-27.0)	178.2 ± 32.7
	B2	260.4 ± 26.8	159.0 (390.0-59.0)	42.0 (153.0-28.0)	178.9 ± 33.5
I405V	I	258.3 ± 31.8	150.0 (425.0-59.0)	42.0 (153.0-28.0)	179.0 ± 33.3
	V	259.6 ± 27.1	145.5 (390.0-59.0)	43.0 (153.0-27.0)	178.0 ± 33.6

Table 10: Pre simvastatin therapy lipid profile of the study cohort based on TaqIB and I405V alleles.

		TC (mg/dl) (Mean ± SD)	TG (mg/dl) (Mean ± SD)	HDL-C (mg/dl) (Mean ± SD)	LDL-C (mg/dl) (Mean ± SD)
Taq1B	B1	180.5 ± 28.4	105.0 (246.0-40.0)	46.0 (95.0-30.0)	110.5 ± 26.9
	B2	184.4 ± 25.9	109.0 (246.0-55.0)	46.0 (95.0-30.0)	115.4 ± 29.1
I405V	I	181.0 ± 27.2	106.0 (246.0-40.0)	46.0 (95.0-30.0)	112.3 ± 29.4
	V	183.6 ± 27.6	106.0 (246.0-57.0)	46.5 (95.0-30.0)	113.5 ± 30.2

Table 11: Post simvastatin therapy lipid profile of the study cohort based on TaqIB and I405V alleles.

		TC (mg/dl) (Mean ± SD)	TG (mg/dl) Median (Range)	HDL-C (mg/dl) Median (Range)	LDL-C (mg/dl) (Mean ± SD)
Taq1B	B1	256.2 ± 29.0	142.5 (390.0-60.0)	42.0 (95.0-26.0)	177.0 ± 23.3
	B2	259.5 ± 26.8	152.0 (390.0-68.0)	41.5 (95.0-29.0)	178.6 ± 23.4
I405V	I	255.9 ± 28.2	144.0 (390.0-60.0)	42.0 (95.0-29.0)	178.1 ± 24.0
	V	259.7 ± 27.0	149.5 (390.0-68.0)	42.5 (95.0-26.0)	178.7 ± 22.7

Table 12: Pre atorvastatin therapy lipid profile of the study cohort based on TaqIB and I405V alleles.

		TC (mg/dl) (Mean ± SD)	TG (mg/dl) (Mean ± SD)	HDL-C (mg/dl) (Mean ± SD)	LDL-C (mg/dl) (Mean ± SD)
Taq1B	B1	176.6 ± 25.7	100.5 (255.0-51.0)	46.0 (83.0-29.0)	108.6 ± 23.6
	B2	179.7 ± 22.7	105.5 (255.0-56.0)	45.5 (83.0-29.0)	110.3 ± 21.3
I405V	I	175.8 ± 24.7	101.5 (255.0-51.0)	46.0 (76.0-29.0)	107.3 ± 23.4
	V	178.5 ± 24.0	106.0 (255.0-51.0)	44.5 (83.0-29.0)	109.7 ± 21.2

Table 13: Post atorvastatin therapy lipid profile of the study cohort based on TaqIB and I405V alleles.

to statin treatment. Even a small difference in the absolute number, for example, in the LDL-C levels after taking one specific statin against one other, can have significant effect on the hard end point, which is the CV event.

Of significant importance is also a probable correlation between the different genotypes and the severity of the side effects of statin treatment.

It would be also of great significance to be confirmed or not, whether it would have a clinical role, the implementation of genetic control before prescribing a statin to a specific patient, in order to choose the most appropriate one for him.

The purpose of this study was to investigate a probable correlation between the two studied polymorphisms of CETP, namely TaqIB and I405V, with better or worse response to two different statins: simvastatin and atorvastatin.

This study has not shown any significant difference at TCHOL, TGs, HDL-C or LDL-C levels before and after treatment with simvastatin and atorvastatin between TaqIB and I405V polymorphisms (concretely among B1B1, B1B2 and B2B2 genotypes of TaqIB polymorphism and among II, IV and VV genotypes of I405V polymorphism). Moreover, no significant difference was revealed studying independently the presence of B1, B2, I, V alleles.

In many cases, pharmacogenetic studies are being criticized for having no consistency to one another and also for their initial selection of the studied genotypes. Undoubtedly, it is not easy for the proper genotype combination to be defined *a priori,* in order to study its impact on a multi-factorial model as the lipidemic profile of the patients.

In this study the selection of the TaqIB and I405V polymorphisms of CETP for their impact on the response to statin treatment was based on previous studies, which have shown a clear correlation between these two polymorphisms and the lipidemic profile, the risk of CAD and the response to hypolipidemic treatment.

The most important part of the planning and the realization of this study was the fact, that the two studied statins were both administered successively to the same individuals. By that means, all the other factors beyond the studied polymorphisms, which probably affect the response of every patient to these statins, were eliminated.

From the other side, the limitations of this study were that its population consisted of 78 individuals and only two polymorphisms of CETP gene were studied. There is the possibility, that different CETP gene polymorphisms would have shown a significant difference in the response of their carriers to simvastatin and atorvastatin.

There is discordance among different pharmacogenetics studies, which investigated the effect of TaqIB polymorphism on response to statin treatment. There are some which showed a significant correlation [17] and others like ours which did not find a significant interaction [25]. However, seeing them as a whole, they have not shown significant differences. This was also the result of a large meta-analysis of Boekholdt et al. [18], which included about 13.000 patients. It did not reveal any significant correlation between the TaqIB polymorphism and a possible difference in response to statin treatment.

Conclusion

In conclusion, current data from pharmacogenetic studies do not support applying a pharmacogenetic control to patients before starting a statin. However, data from multicenter Genome-Wide Association Studies (GWAS), which would focus on the role of CETP polymorphisms at the response to different statins but also on their possible toxicity, are needed before we abandon definitely the genetic guided statin treatment.

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