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Lack of Atorvastatin Protective Effect Against Atrial Fibrillation in CETP TaqIB2B2 Genotype

Francesca Galati[1], Antonio Galati[2], Serafina Massari[1]

[1]Department of Biological and Environmental Sciences and Technologies – University of Salento, Lecce, Italy. [2]Department of Cardiology – "Card. G. Panico" Hospital, Tricase, Lecce, Italy.

Abstract

There has been some evidence for a role of statins in reducing the risk of atrial fibrillation, but the response to statin treatment varies considerably due to environmental and genetic factors. One of these is related to CETP expression.

So we assessed whether CETP TaqIB polymorphism influences atrial fibrillation occurrence after treatment with statins.

200 unrelated dyslipidemic Caucasian patients (146 men and 54 women; mean age 75±8) from Salento (Southern Italy), assigned to atorvastatin treatment, and 158 normolipidemic subjects (119 men and 39 women; mean age 75±11), selected from the same ward, were enrolled. All patients were followed at six-month intervals. CETP TaqIB polymorphism was genotyped by RFLP-PCR.

During a mean follow-up time of 71±6 months, 64 patients (32%) of the group treated with atorvastatin and 70 subjects (44%) of the group without atorvastatin experienced at least one episode of AF, with a statistically significant difference (p = 0,0208) between the two groups. No significant differences were observed between the two groups with regard to demographic and echocardiographic data, to clinical history and pharmacological treatment. While in patients not assuming atorvastatin there was no significant difference (p = 1) between TaqIB genotype and atrial fibrillation occurence, in subjects treated with atorvastatin B2B2 genotype was more frequent in patients with atrial fibrillation (p = 0,0001). According to these data the subjects with the B2B2 genotype seem to be more susceptible to atrial fibrillation development (RR 2,74; IC 95% 1,92-3,90; p<0.025).

Our data seem to provide a further evidence for the hypothesis that statins may have adverse effect in subjects with genetically low CETP levels. Because statins reduce CETP activity up to 30%, we hypothesize that such CETP activity reduction by statins, in patients with low CETP levels induced by polymorphism, may counteract the beneficial effect of statins on atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice and its prevalence increases with age. Although not acutely life threatening, because of haemodynamic compromise and associated increased risk of stroke, it can cause severe morbidity and mortality, especially among older people and those with heart failure. Therefore it leads to worsening of quality of life and causes a substantial burden to health services.

Recently, there has been some evidence for the protective role of statins in reducing the risk of this arrhythmia. In particular, one meta-analysis suggested that statins could reduce the risk of atrial fibrillation by 61%.[1] A second meta-analysis, however, yielded a more modest (and non-significant) point estimate of 24%.[2]

There is a considerable variation in the response to statin treatment,[3] due to environmental and genetic factors. One of these is related to expression of cholesteryl ester transfer protein (CETP), which plays a key role in lipid metabolism. In fact the statin efficacy may vary due to patients CETP genotype[4,5] and CETP concentration.[6]

Several single nucleotide polymorphisms (SNPs) in the CETP gene have been identified. The most widely studied CETP variant is denoted TaqIB (rs708272), affecting the 279th nucleotide in the first intron of the gene.[7]

In the REGRESS study[8] an interaction between this polimorphism and efficacy of statin therapy was observed, with TaqIB1 allele associated to a better response to statins. Carlquist also observed a pharmacogenetic interaction for coronary atherosclerotic events,[9] but the observed effect was opposite, because cardiovascular event reduction by statin therapy is enhanced in the presence of TaqIB2 allele. Instead, an individual patient meta-analysis of 13677 patients[10] failed to demonstrate an influence of this CETP variant on the response to pravastatin therapy.

High CETP activity, as seen in B1B1 patients, is classically known to increase the cholesterol component of atherogenic lipoprotein. Statins reduce CETP activity up to 30%[11,12] and this reduction is associated with beneficial effects in subjects with high CETP concentrations, while these effects lack in B2B2 patients, with genetically determined low CETP activity.[4] In fact, a critical concentration of CETP is required for normal reverse cholesterol

Disclosures:
None.

Corresponding Author:
Dr. Francesca Galati
Department of Biological and Environmental Sciences and Technologies, University of Salento
S.P. 6, Lecce-Monteroni
Lecce, Italy.

Table 1: Demographic data and clinical and echocardiographic features of the study population

		Atorvastatin n =200	No atorvastatin n = 158	p value
Demographic	Male sex, n (%)	146 (73%)	119 (75%)	0,6298
	Age (years)	75±8	75±11	1,0000
	BMI (kg/m2)	28±3	27±4	0,0072
	Current smoking	96 (48%)	73 (46%)	0,7501
Clinical history	NYHA class, n (%)			0,9134
	I	122 (61%)	95 (60%)	
	II	78 (39%)	63 (40%)	
	IHD, n (%)	99 (49%)	79 (50%)	1,0000
	Hypertension, n (%)	151 (75%)	113 (72%)	0,4002
	COPD, n (%)			0,9877
	Mild	44 (22%)	36 (23%)	
	Moderate	125 (62%)	100 (63%)	
	Severe	24 (12%)	17 (11%)	
	Very severe	7 (4%)	5 (3%)	
Echo	AP left atrial diameter, mm	45,4±6,5	44,8±6,3	0,3800
	SI left atrial diameter, mm	52,5±6,2	53,1±3,6	0,2805
	ML left atrial diameter, mm	37,4±5,6	38,1±4,9	0,2157
	Atrial volume, cc	47,0±1,2	46,7±2,5	0,1583
	LV EF, (%)	56±7	55±4	0,1103

BMI, body mass index; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease; AP, antero-posterior; SI, supero-inferior; ML, medio-lateral; LV EF, left ventricular ejection fraction

transport.

Therefore, we conducted a prospective study to assess whether CETP TaqIB polymorphism influences the occurrence of atrial fibrillation in subjects treated with statins.

Materials and Methods

Subjects

200 unrelated dyslipidemic Caucasian patients (146 men and 54 women; mean age 75±8) from Salento (Southern Italy) and 158 normolipidemic subjects (119 men and 39 women; mean age 75±11), selected from the same ward, were enrolled between January 2007 and June 2009. Dyslipidemia was defined as elevated total (>240 mg/dL) or low-density lipoprotein (LDL - >130 mg/dL) cholesterol levels, or low levels of high-density lipoprotein cholesterol (HDL - <40 mg/dL) or elevated triglycerides levels (>150 mg/dL). All subjects were on a stable medication regimen and diet for at least 4 weeks prior to study screening. Patients with a history of stroke, renal disease, diabetes mellitus, heart failure (greater than grade NYHA II), hyperthyroidism, moderate to severe valve disease and lone AF were excluded. The dyslipidemic subjects were assigned to atorvastatin treatment for at least 6 months. The dose of atorvastatin (10-40 mg/day) was adjusted according to the National Cholesterol Education Program Adult Treatment Panel III.[13] All patients were followed up in our outpatient clinic at six-month intervals.

The presence of AF was determined by ambulatory electrocardiograms or 24 hours ECG monitoring. Transthoracic echocardiogram was performed to asses left atrial and left ventricular dimensions, atrial volume, left ventricular ejection fraction and to detect significant valvular heart disease (at least moderate to severe).

The study was approved by the local ethics committee and conducted in accordance with the guidelines of the declaration of Helsinki. An informed consent prior to participation was obtained from all subjects.

Laboratory Measurements

The urinary albumin excretion rate was measured as the mean of two 24-h urine collections, and urinary albumin concentrations were determined by nephelometry. Blood samples were collected from subjects, after a 12- to 14-hour fast, into tubes containing 0.1% EDTA. High-sensitive C-reactive protein (CRP) was determined by nephelometry, interleukin-6 (IL-6) by immunochemioluminescence, total serum cholesterol, HDL-cholesterol and triglycerides by colorimetric/ spectrophotometric procedure, whereas LDL-cholesterol was calculated using the Friedewald equation.

DNA Analysis

DNA extraction was carried out on total blood using Archive Pure DNA Blood Kit (5-PRIME, Hamburg, Germany) according to the manufacturer's recommended protocol. Subsequently, CETP TaqIB (rs708272, G/A) genotyping was performed in all participants. Briefly, a fragment of 1018 bp of the intron 1 of the gene was amplified by PCR (polymerase chain reaction) with the use of primers designed on the NCBI Reference Sequences NT_010498 (pos 10608262-10610237) (forward 5'-GTGTGCCGCATCACCAAG-3', reverse 5'-TCTCGCCGTGATATCTG-3') followed by TaqI digestion. The resulting DNA fragments were the 707 and 311 bp in length corresponding to the wild type B1 allele, and the intact 1018-bp in length corresponding to the uncut B2 allele.

Statistical Analysis

Continuous data are expressed as mean ± standard deviation; categorical data are expressed as a percentage. A goodness of fit test for normality and a Brown-Forsythe or Levene test for homogeneity of variances were used to assess the applicability of parametric tests. Differences between mean data were compared by Student's t-test for the normally distributed continuous variables or by the Mann-Whitney test for non-normally distributed variables. Differences in genotype frequencies and other categorical data between cases

Table 2: Laboratory data of the study population

	Atorvastatin		No atorvastatin	p value	
	Before therapy	After therapy			
C-reactive protein, mg/dl	1,12±2,10	0,99±3,21	1,02±1,83	0,6364*	0,9166#
Urinary albumin excretion, mg/L	85,53±216,25	69,87±184,52	64,73±127,38	0,3361*	0,7656#
IL-6, pg/ml	14,48±56,62	16,67±58,97	16,35±41,02	0,7273*	0,9538#
Total cholesterol, mmol/L	5,97±0,29	5,03±0,58	4,59±1,03	0,0001*	0,0001#
Triglycerides, mmol/L	2,02±0,38	1,74±0,45	1,23±0,59	0,0001*	0,0001#
HDL-cholesterol, mmol/L	1,00±0,21	1,30±0,32	1,47±0,40	0,0001*	0,0001#
LDL-cholesterol, mmol/L	4,05±0,38	2,95±0,71	2,51±0,92	0,0001*	0,0001#

IL-6, interleukin 6

* p value between pts on atorvastatin before therapy and pts not assuming atorvastatin; # p value between pts on atorvastatin after therapy and pts not assuming atorvastatin

Table 3: TaqIB polymorphism: genotype frequency

	Total population	Atorvastatin	No atorvastatin	p value
B2B2	62 (17%)	33 (16%)	29 (18%)	
B1B2	164 (46%)	87 (44%)	77 (49%)	0,3850
B1B1	132 (37%)	80 (40%)	52 (33%)	

Table 4: Atrial fibrillation occurrence and statin therapy

	Atorvastatin	No atorvastatin	p value
Atrial fibrillation	64 (32%)	70 (44%)	0,0208
No atrial fibrillation	136 (68%)	88 (56%)	

and controls were compared with Fisher's exact test (mid-p exact p-value). Differences in baseline characteristics, inflammation and lipid metabolism parameters between the three polymorphic forms of the CETP gene were analyzed by ANOVA. The consistency of the genotype frequencies with the Hardy-Weinberg equilibrium (HWE) was tested using a chi-squared goodness-of-fit test on a contingency table of observed versus expected genotypic frequencies in cases and controls. Post-hoc evaluations, where necessary, were performed by means of the Bonferroni correction. A two-sided p value <0.05 was considered significant for all tests.

Results

Table 1 provides a summary of the characteristics of our population. The two groups appear to be homogeneous. No differences exist with regard to demographic data, clinical history and echocardiographic measurements, with the exception of higher body mass index in the group assuming atorvastatin. Particularly 73,7% of the total population was hypertensive, but hypertension was distributed in an uniform manner between the two groups (75% vs 72%). No significant difference in pharmacological treatment (beta-blockers, ACE-inhibitors, angiotensin receptor blockers, antialdosterone, amiodarone, propafenone) was observed between the groups. The average dosage of atorvastatin was similar in patients with and without atrial fibrillation. The laboratory data concerning inflammation (C-reactive protein, urinary albumin excretion and interleukin 6) were not different between the two groups, while the lipid metabolism data were higher in patients taking atorvastatin, both before therapy and after the start of statin therapy (Table 2).

The distribution of CETP TaqIB polymorphism in the whole population and in the two groups is shown in table 3. B1 and B2 were respectively used to denote the presence and the absence of the restriction site for the enzyme TaqI in intron 1. No statistically significant difference was evidenced between the two groups. Hardy-Weinberg equilibrium was reached in the whole population as in the two study groups.

During a mean follow-up time of 71±6 months, 64 patients (32%; 95%CI 0,26-0,39) of the group treated with atorvastatin and 70 subjects (44%; 95%CI 0,37-0,52) of the group without atorvastatin experienced at least one episode of AF, with a statistically significant difference (p = 0,0208) between the two groups (Table 4): administration of atorvastatin was associated with a lower frequency of atrial fibrillation occurrence.

The genotypic distribution of the polymorphism with respect to arrhythmia occurrence is reported in Table 5 and 6. While in patients not assuming atorvastatin there was no significant difference (p = 1) between TaqIB genotypes and atrial fibrillation occurence, in subjects treated with atorvastatin B2B2 genotype was more frequent (p = 0,0001) in patients with atrial fibrillation, 23 subjects (36%; 95%CI 0,25-0,48) vs 11 subjects (8%; 95%CI 0,04-0,14). According to these data the subjects with the B2B2 genotype seem to be more susceptible to atrial fibrillation development (RR 2,74; IC 95% 1,92-3,90; p<0.025).

When analyzed by allele status (Tables 7 and 8), there were no significant differences in baseline clinical characteristics between TaqIB2B2 patients and B1 carriers (B1/B2 plus B1/B1) in both groups, with the exception of higher atrial volume (p = 0,0142) in B1 carriers assuming atorvastatin. With regard to laboratory data (Tables 9 and 10) the only significant difference was represented by higher total cholesterol levels in B2/B2 patients not assuming atorvastatin (p = 0,0001). This was associated with higher HDL-C levels (p = 0,0378), while there was no difference regarding the LDL-C values (p = 0,3706).

Discussion

We assessed whether CETP TaqIB polymorphism modified the onset of atrial fibrillation in subjects treated with atorvastatin. Indeed statins seem to have a protective effect on atrial fibrillation onset. Such beneficial action was also documented in our population: patients assuming atorvastatin had a significant lower occurrence of atrial fibrillation. But there is consisting evidence that genetic markers, such as single nucleotide polymorphisms, related to candidate genes which impact metabolisms, enzymes, transport systems, may modify the response to statin therapy. CETP plays a major role in modifying lipoprotein particles and CETP TaqIB polymorphism, associated with changes in CETP activity and mass, seems to modulate the plasma lipid profile and the risk of cardiovascular events in subjects taking statins. In our study we did not measured CETP mass or activity across genotype subgroups, but previous studies, conducted in hyperlipidaemic and normolipidaemic subjects, confirmed that CETP activity and mass were lower in B2B2 genotype compared with the others (B1B1 and B1B2).[14,15,16]

The frequency of the TaqIB polymorphism in our study cohort was similar to that reported in other populations[16,17] suggesting that our subjects are not genetically different from others.

Our data show that this polymorphism seems to cancel the protective role of statins in reducing the risk of atrial fibrillation. Many studies are being conducted all over the world to determine the differential responses to lipid lowering treatment as a function of CETP TaqIB genotype. In one such a study, the influence of CETP TaqIB/-629C/A genotypes on atorvastatin treatment in type 2 Diabetes Mellitus was studied and B1B1/CC carriers have been found to have more atherogenic lipid profile, including low HDL-C levels, but they were found to be better responders to statin therapy.[5] In REGRESS study, pravastatin therapy slowed the progression of coronary atherosclerosis in B1B1 carriers but not in B2B2.[4] In our study we also confirmed an interaction between statins and TaqIB polymorphism, for the first time in patients with atrial fibrillation, in which we found a higher percentage of B2B2 genotype. Thus the benefit of statin therapy seems to be restricted to B1 patients. Instead, in patients not taking atorvastatin we did not observe any

Table 5: TaqIB polymorphism: genotype frequency in patients not assuming atorvastatin

	AF	No AF	p value
B2B2	13 (19%)	16 (18%)	1,0000
B1 carriers	57 (81%)	72 (82%)	

Table 6: TaqIB polymorphism: genotype frequency in patients assuming atorvastatin

	AF	No AF	p value
B2B2	23 (36%)	11 (8%)	0,0001
B1 carriers	41 (64%)	125 (92%)	

Table 7: Clinical characteristics and events stratified according to CETP allele status in patients not assuming atorvastatin

		CETP B2/B2 n = 29	CETP B1 carriers n = 129	p value
Demographic	Male sex, n (%)	22 (76%)	97 (75%)	1,0000
	Age (years)	74±12	75±11	0,6642
	BMI (kg/m2)	26±4	27±4	0,2258
	Current smoking	13 (45%)	62 (48%)	0,8381
Clinical history	NYHA class, n (%)			1,0000
	I	18 (62%)	77 (60%)	
	II	11 (38%)	52 (40%)	
	IHD, n (%)	16 (55%)	64 (50%)	0,6824
	Hypertension, n (%)	21 (72%)	95 (74%)	1,0000
	COPD, n (%)			0,9792
	Mild	7 (24%)	29 (22%)	
	Moderate	18 (62%)	82 (64%)	
	Severe	3 (10%)	14 (11%)	
	Very severe	1 (4%)	4 (3%)	
Echo	AP left atrial diameter, mm	44,7±6,5	46,1±5,8	0,2525
	SI left atrial diameter, mm	52,1±6,5	52,6±5,2	0,6563
	ML left atrial diameter, mm	37,0±5,1	37,7±5,8	0,5496
	Atrial volume, cc	46,4±2,0	46,5±1,9	0,7072
	LV EF, (%)	55±6	56±7	0,4773

BMI, body mass index; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease; AP, antero-posterior; SI, supero-inferior; ML, medio-lateral; LV EF, left ventricular ejection fraction

Table 8: Clinical characteristics and events stratified according to CETP allele status in patients assuming atorvastatin

		CETP B2/B2 n = 33	CETP B1 carriers n = 167	p value
Demographic	Male sex, n (%)	24 (73%)	122 (73%)	1,0000
	Age (years)	76±5	74±8	0,1685
	BMI (kg/m2)	27±3	28±3	0,0817
	Current smoking	16 (48%)	80 (48%)	1,0000
Clinical history	NYHA class, n (%)			1,0000
	I	20 (61%)	102 (61%)	
	II	13 (39%)	65 (39%)	
	IHD, n (%)	16 (48%)	85 (51%)	0,2915
	Hypertension, n (%)	26(79%)	125 (75%)	0,8249
	COPD, n (%)			1,0000
	Mild	7 (21%)	37 (22%)	
	Moderate	21 (64%)	104 (62%)	
	Severe	4 (12%)	20 (12%)	
	Very severe	1 (3%)	6 (4%)	
Echo	AP left atrial diameter, mm	44,8±6,3	46,5±5,3	0,1046
	SI left atrial diameter, mm	51,9±5,1	53,6±6,5	0,1579
	ML left atrial diameter, mm	36,8±5,1	38,3±4,8	0,1061
	Atrial volume, cc	46,8±1,8	48,5±3,8	0,0142
	LV EF, (%)	56±4	55±4	0,1909

BMI, body mass index; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease; AP, antero-posterior; SI, supero-inferior; ML, medio-lateral; LV EF, left ventricular ejection fraction

difference between the various genotypes regarding the occurrence of atrial fibrillation. This does not conflict with what we affirmed in a previous work,[18] in which we documented a higher risk of atrial fibrillation in patients with B2B2 genotype, as this was only true for the female subjects, while the population object of our study is made for 3/4 of male subjects. The high frequency of appearance of atrial fibrillation can be explained by old age of our population and the high percentage of patients with hypertension.

We should expect the B2B2 genotype would impair statins ability to reduce CRP or the impact on the LDL-C lowering effect. But our data are not consistent with that. In fact, in subjects assuming atorvastatin, lipid parameters among CETP TaqIB genotypes were not different, though our patients with B2B2 genotype had a higher event risk compared to B1 carriers.

CETP simultaneously affects the concentration and composition of both antiatherogenic and atherogenic lipoproteins. So we must take into account the net effect of CETP activity, likely dependent on the metabolic, genetic, and environmental context. CETP also regulates the cholesterol traffic directly at cellular level, plays a role in macrophage cholesterol homeostasis,[19] contributes to the genesis of small preβ-HDL, which stimulate cellular cholesterol efflux from macrophages and fibroblasts. Furthermore, cholesterol can change opening/closure state of voltage-dependent ion channels forming functional units with lipids in close proximity.[20]

We do not assume a negative effect of the polymorphism on statins, but we hypothesize particularly low CETP levels arising from a "double inhibition" of CETP (by statins and by polymorphism). Whereas in subjects with defective apoB-lipoprotein clearance CETP might be harmful, instead in those with highly effective apoB-lipoprotein clearance (such in patients on statins) CETP action seems to be advantageous. But the important reduction in CETP levels, resulting from the combined action of polymorphism and statins, might delete these positive effects, promoting the onset of atrial fibrillation. Data from CETP inhibitors trials (with all

Table 9: Laboratory data stratified according to CETP allele status in patients assuming atorvastatin

	Before statin therapy			After statin therapy		
	B2/B2 n = 33	B1 carriers n = 167	p value	B2/B2 n = 33	B1 carriers n = 167	p value
C-reactive protein, mg/dl	1,01±2,0	1,18±2,6	0,7229	0,95±3,0	1,02±3,7	0,9187
Urinary albumin excretion, mg/L	83,24±199,32	89,21±233,96	0,8912	68±194,26	72,47±183,21	0,8992
IL-6, pg/ml	12,35±59,23	15,38±54,67	0,7745	14,99±62,21	16,79±57,11	0,8707
Total cholesterol, mmol/L	6,04±0,26	5,96±0,29	0,1427	5,02±0,49	5,04±0,60	0,8574
Triglycerides, mmol/L	2,02±0,42	2,02±0,38	1,0000	1,70±0,48	1,74±0,44	0,6388
HDL-cholesterol, mmol/L	0,98±0,23	1,00±0,22	0,6363	1,30±0,33	1,30±0,32	1,0000
LDL-cholesterol, mmol/L	4,13±0,38	4,04±0,38	0,2152	2,93±0,68	2,95±0,72	0,8832

IL-6, interleukin 6

Table 10: Laboratory data stratified according to CETP allele status in patients not assuming atorvastatin

	B2/B2 n = 29	B1 carriers n = 129	p value
C-reactive protein, mg/dl	0,91±1,48	1,05±1,91	0,7117
Urinary albumin excretion, mg/L	48,91±80,51	68,34±135,98	0,4606
IL-6, pg/ml	15,7±24,5	16,5±43,7	0,9243
Total cholesterol, mmol/L	4,81±1,10	4,54±1,00	0,0001
Triglycerides, mmol/L	1,25±0,63	1,23±0,58	0,8690
HDL-cholesterol, mmol/L	1,61±0,37	1,44±0,40	0,0378
LDL-cholesterol, mmol/L	2,64±0,88	2,47±0,93	0.3706

IL-6, interleukin 6

patients receiving statin treatment) seem to support our hypothesis, as, despite a substantial increase in HDL cholesterol levels, no net benefits or harm was evident.[21,22,23]

Clearly, the relationship between plasma HDL and atherosclerosis is a more complex one than merely 'high levels are good'.

A limitation of our study may be represented by the low number of the enrolled patients. Despite this, our work was performed on patients from a well-defined geographical area and in these association studies the genetic background is particularly important.

Conclusion

Our study seems to show an interaction among CETP genotypes, statins and occurrence of atrial fibrillation. We hypothesize that further CETP suppression by statins in subjects with already intrinsically low CETP levels, induced by polymorphism, could have a deleterious effect on clinical outcome (i.e. atrial fibrillation).

However, to better define the associations observed in our work, further studies are required in larger populations, also belonging to other geographical areas.

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