INFLUENCE OF THE HMG-CoA REDUCTASE (TTA)n REPEAT GENE POLYMORPHISM ON THE EFFECTS OF ATORVASTATIN IN CORONARY ARTERY DISEASE PATIENTS

Viviana Noriega MSc[a,b], Chistian Pennanen MSc[a,b], Maria Pilar Sánchez MSc[b] , Mario Chiong MSc[a,b], Marcelo Llancaqueo MD[d],Sergio Lavandero PhD[a,b,c] and Juan Carlos Prieto MD[c,d*]

[a]FONDAP Center for Molecular Studies of the Cell, [b]Faculty of Chemical and Pharmaceutical Sciences, [b,c]Institute of Biomedical Sciences, Faculty of Medicine and [e] [d]Cardiovascular Center, Clinical Hospital, University of Chile, Santiago, Chile.

This work was supported in part by a Grant from Saval S.A, Medical Chilean Society (to J.C.P.) and FONDAP Grant 15010006 (to S.L.)

Short title: Polymorphism HMGCR in coronary artery disease patient.

Running title**:** polymorphism HMG-CoA and cholesterol levels

*Corresponding authors: Juan Carlos Prieto MD, Cardiovascular Center, Clinical Hospital, Universidad de Chile, Santos Dumont 999, Santiago 8380492, Chile. Tel: +562-978-6044; E-mail: jprieto@med.uchile.cl or Sergio Lavandero PhD, FONDAP Center for Molecular Studies of the Cell, Faculty of Chemical and Pharmaceutical Sciences, Olivos 1007, Santiago 8380492, Chile. Tel: +562-978-2903; E-mail: slavander@uchile.cl

Background Inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase have been clinically used for lowering total and low-density lipoprotein cholesterol (LDL-C). Interindividual pharmacological differences observed with this treatment have been attributed to genetic differences. The aim of the present study was examined the association between, LDL-C reduction by atorvastatin and (TTA)n repeat polymorphism in the HMG-CoA reductase gene (HMGCR) in patients with coronary artery disease (CAD). Also, changes in levels of total cholesterol, high sensitivity C-reactive protein (hsCRP) and free F_2-isoprostanes induced by atorvastatin and their association with the (TTA)n polymorphism was also assessed.

Methods Sixty-four patients with documented CAD completed the trial receiving 40 mg of atorvastatin daily for 8 weeks. Lipid levels as, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and serum triglyceride levels were determined using enzymatic methods. LDL-C was calculated using the Friedewald´s formula. The hsCRP levels were determined by latex method assay and free F_2-isoprostanes were performed using enzyme immunoassay (EIA). Genotyping was done by the polymerase chain reaction.

Results The genotype distribution of the HMGCR (TTA)n polymorphism was: >10/>10 in 22 of 64 patients (34%), >10/10 in 14 of 64 patients (22%) and 10/10 in 28 of 64 patients (44%). Atorvastatin significantly reduced LDL-C levels in all patients ($p<0.0001$), regardless the type of HMGCR (TTA)n polymorphism. Reduction on hsCRP were observed in atorvastatin-treated patients with HMGCR (TTA)n alleles >10/>10 and 10/10 ($p<0.05$). Free F_2-isoprostanes and total cholesterol were also reduced significantly after treatment for all alleles ($p<0.001$).

Conclusions In a sample of patients with chronic stable CAD, no associations were found in the atorvastatin-induced reduction of LDL-C, total cholesterol, hsCRP and free F_2- isoprostanes with the HMGCR (TTA)n polymorphism.

Therapy with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), is widely used in the treatment of hypercholesterolemia, lowering the total and low-density lipoprotein cholesterol (LDL-C). Statins therapy also lowers C-reactive protein (CRP) levels in a LDL cholesterol-independent manner (1-7). Statins also have antioxidant properties (8), and is prescribed for both, primary (9-11) and secondary (12-16) prevention of coronary artery disease (CAD). However, considerable interindividual variation exists in response to statin therapy (17). Studies about genetic variations in HMG-CoA reductase gene (HMGCR), the direct target of statin therapy, and the relation with the changes in lipid levels with statin therapy are limited (18,19). Previous studies have indicated that variable number of tandem repeats (VNTR) polymorphism (TTA)n of the HMGCR gene was associated with pathologies such as CAD and hypercholesterolemia (20,21). Moreover, it has been reported an almost significant difference between the (TTA)n repeat polymorphism in the HMGCR gene and cholesterol absorption in response to plant stanol consumption (22).

The aim of the present study was to evaluate the role of HMG-CoA reductase gene (HMGCR) (TTA)n repeat polymorphism in relation to the LDL-C lowering efficacy of atorvastatin in Chilean patients with CAD. A secondary objective was to determine the change in levels of total cholesterol, high-sensitivity CRP (hsCRP) and free F_2-isoprostanes after atorvastatin treatment and its relation with the presence of HMGCR (TTA)n polymorphism in patients with CAD.

Methods

Study design and patient selection

This study was composed of 69 patients who were obtained from the database of Cardiovascular Center, Clinical Hospital, University of Chile, these patients had history of coronary heart disease treated with coronary artery bypass grafting (CABG) or angioplasty. This study was an open study where one daily dosing of 40 mg atorvastatin (Saval S.A. Chile) was administered for 8 weeks. Medical history and current medications were recorded at the first visit. Physical examination was performed and a dietary approach was given. At the follow-up, potential adverse effects were registered at each visit. This study was approved by the Ethics Committee of the Clinical Hospital of the University of Chile (Santiago, Chile) and all patients gave their informed consent.

Subjects

Male and female patients, >18 years-old with angiographically documented CAD, baseline levels of LDL-C 100 to 220 mg/dL, triglyceride levels <400 mg/dL, with no use of statins during 2 months previous to the enrollment, and without contraindications to statin therapy. Subjects were excluded if they had been hospitalized within 90 days with an acute coronary syndrome, undergone coronary revascularization procedure within 90 days, or had a known acute or long-term inflammatory process. Additionally, patients with active liver disease or dysfunction determined by hepatic transaminase ≥ 2 fold normal upper limit, serum creatine kinase level > 3 fold normal upper limit and serum creatinine > 2.0 mg/dL, were excluded. Test for pregnancy was not performed because all patients were in post-menopause.

Laboratory testing

As part of the protocol, venous blood was obtained at baseline and after 8 weeks for lipids levels, hsCRP and free F_{-2} isoprostanes. The hsCRP levels were determined by an assay from Dade-Behring (Deerfield, IL) (23) and free F_2-isoprostanes were determined as described by Pradelles *et al.* (24). Lipid levels were determined using enzymatic methods. Low-density lipoprotein cholesterol was calculated using the Friedewald formula (25).

Genotyping

Genomic DNA was extracted from a whole blood sample using standard extraction procedures. Genotyping for the (TTA)n repeat polymorphism within the intron 2 of the HMGCR gene was performed by a polymerase chain reaction (PCR) according to Lalovic *et al* (26). Seven different products ranging from 175-193 bp were amplified using the primers 5´CAGAGTGACACTCTGTCTCC-3´ and 5´CATGTTCCATCCATGTCTGC-3´, corresponding to 10 to 16 repeats of the triplet TTA. Therefore, patients were divided into 3 categories. The first group had two alleles with more than 10 TTA repeats (>10/>10), the second group one allele >10 and the other allele with 10 TTA repeats (<10/10), and the third group had two alleles with 10 TTA repeats (10/10).

Statistical analysis

Hardy-Weinberg equilibrium was assessed using the χ^2 test. The genotype frequency were in Hardy-Weinberg equilibrium.

The primary comparison of this study was the reduction magnitude in LDL-C at 8 weeks versus the presence the different (TTA)n polymorphisms in the HMGCR post-treatment with atorvastatin.

Categorical data were analyzed using chi-square test or Fisher's exact test as indicated. Differences in continuous variables were evaluated by Student's test, one-way analysis of variance or the Kruskal Wallis rank test. Nonparametric testing (Kruskal Wallis rank test) was used to assess differences in changes in the baseline. Data were reported as mean and SD. For PCR also were reported the medians. The statistical significance was set at $p<0.05$.

Enrollment of 64 patients was designed to provide 80% power significance (α) level of 0.05 to detect a 20% difference in LDL-C levels in >10/>10 (TTA)n polymorphism compared with 10/10 repeat.

Results

Characteristics of study population

Ninety-four patients were screened, and 69 met LDL-C and other inclusion criteria. Two patients were withdrawal, one for angioedema and other for being diagnosed gastric cancer, two weeks after he entered the study and three patients were lost at the follow-up. Sixty-four patients completed the 8 week statin treatment period. Baseline characteristics of the 64 evaluated subjects are presented in Table I.

The genotype distribution of the HMGCR (TTA)n polymorphism was as follows: 22 of 64 patients (34%) were >10/>10 allele, 14 of 64 patients (22%) were >10/10 allele and 28 of 64 patients (44%) were 10/10 allele (Table II). The 3 groups had homogeneous baseline characteristics (Table I).

Changes in LDL-C and total serum cholesterol

The primary end point was the change in the LDL-C by atorvastatin, in relation to baseline (Table III). At the end of 8 weeks, LDL-C levels were significantly lower with a percent change of -46.1, -45.6 and -44.5 for the groups patients >10/>10, >10/10 and 10/10, respectively ($p<0.0001$; Figure 1). Also, total serum cholesterol levels were significantly lower in relation to basal values with a percent change of -35.1, -32.3 and -33.7 for the groups patients >10/>10, >10/10 and 10/10, respectively ($p<0.0001$; Figure 2). Overall statistical testing showed that these responses were not different between groups of patients with different (TTA)n polymorphism, with p value 0.743 for LDL-C and p value 0.117 for total cholesterol.

Changes in hsCRP and free F_2-isoprostanes:

Changes in hsCRP and free F_2-isoprostanes by atorvastatin are presented in Table III. At the end of 8 weeks, hsCRP levels were significantly lower with a mean change of -1.22 and -0.94 mg/L for the groups patients >10/>10 and 10/10 respectively ($p<0.05$). Also, free F_2-isoprostane levels were significantly lower in relation to basal values with a percent change of -41.9, -38.2 and -44.9 for the groups patients >10/>10, >10/10 and 10/10 respectively (p value <0.001). Overall statistical testing showed that these responses were not different between the patients groups with different (TTA)n polymorphism with p value 0.406 for hsCRP and p value 0.542 for free F_2-isoprostanes.

Discussion

In the present study, we examined the association between LDL-C reduction by atorvastatin and (TTA)n repeat polymorphism in the HMGCR gene in patients with CAD. We also assessed atorvastatin-induced change of levels of total cholesterol, hsCRP, free F-$_2$isoprostane and their association with the (TTA)n polymorphism.

Our main observations were 1) the allele frequencies were different to the observed in another population, Plat et al report that the genotype distribution of the HMGCR (TTA)n polymorphism was 21.4% for >10/>10 allele, 47.3% for >10/10 allele and 31.3% for 10/10 allele, in our population the genotype distribution was 34% for >10/>10 allele, 22% for >10/10 allele and 44% for 10/10 allele. 2) the magnitudes of reduction of both LDL-C and total cholesterol were not different between the allelic variants 3) atorvastatin treatment induced hsCRP and free F_2-isoprostane reduction.

Previous studies have indicated that variable number of tandem repeats (VNTR) polymorphism (TTA)n of the HMGCR gene was associated with pathologies such as CAD and hypercholesterolemia (20,21). Moreover, it has been reported an almost significant difference between the (TTA)n repeat polymorphism in the HMGCR gene and cholesterol absorption in response to plant stanol consumption (22).

Although atorvastatin is widely prescribed for the treatment of hypercholesterolemia, it displays marked interindividual variability in lipid-lowering efficacy (17). Genetics variation in HMGCR, the direct target of statin therapy, is surprisingly understudied. The PRINCE (the Pravastatin Inflammation/CRP Evaluation) that reported two non-coding HMGCR variants in tight linkage disequilibrium (SNPs12 and 29) associated with the magnitude of total cholesterol and LDL-C response. Carriers of the haplotype constituted by these SNPs displayed smaller reductions in LDL-C than non-carriers (18). Even so, association between these HMGCR SNPs and LDL-C response failed to replicate in the ACCESS cohort (19). Aside from the PRINCE

and ACCESS, there are but no pharmacogenetics studies that have studied the HMGCR and the response to statins. Our findings showed no relationship between the reduction of LDL-C levels and the (TTA)n repeat polymorphism. In fact, very small differences in percent change of the LDL-C were observed among the three groups of patients with the (TTA)n polymorphism. In particular neither SNP or the (TTA)n polymorphism alter the function or expression of HMGCR. The other important consideration is that, PRINCE and ACCESS pharmacogenetics studies included patients of other ethnic group different from ours.

In the current analysis, we found that statins decreased hsCRP levels, reflecting its anti-inflammatory effects beside the lipid-lowering action (27). To evaluate oxidative stress, the levels of free F_2-isoprostanes were measured. A reduction of the plasma levels of this biomarker was observed independently of patients' haplotype.

A significant limitation of our study is that only a single statin was tested, besides the study tested only one dose. However, the dose of atorvastatin used is high, compared to dose routinely given for this agent. Moreover, this study was relatively small, and requires to be replicate in larges prospective cohorts of patient

In conclusion LDL-C and total cholesterol concentrations, as well as their changes after treatment with atorvastatin, were not related to presence in the HMGCR polymorphism (TTA)n. Futures studies may determine whether this small difference in the cholesterol reduction that there is between the genotypes, could be explained by dose adjustment. Data from pharmacogenetics studies are expected to have great impact in the clinical area in the future and will allow the identification of people likely to get the greatest and least benefit from a given intervention.

References

1. Ridker PM, Rifai N, Pfeffer MA. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Circulation 1998; 98: 839-44.
2. Ridker PM, Rifai N, Clearfiel M. Measurement of C-reactive protein for the targeting of statins therapy in the primary prevention of acute coronary events. N Engl J Med 2001; 344: 1959-65.
3. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwal E. Long-term effects of pravastatin on plasma concentration of C-reactive protein . Circulation 1990; 100: 230-5.
4. Albert MA, Danielson E, Rifai N, Ridker PM. Effects of statin therapy on C-reactive protein levels: the Pravastatin Inflammation/CRP Evaluation (PRINCE): a randomized trial and cohort study. JAMA 2001; 286: 64-70.
5. Ridker PM, Rifai N, Lowenthal SP. Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. Circulation 2001; 103: 1191-3
6. Kinlay S, Timmis T, Clark M. Comparison of effect of intensive lipid lowering with atorvastatin to less intensive lowering with lovastatin on C-reactive protein in patients with stable angina pectoris and inducible myocardial ischemia. Am J Cardiol 2002; 89: 1205-7.
7. Jialal I, Stein D, Balis D. Effects of hydroxymethyl glutaryl coenzyme A reductase inhibitors therapy on high sensitive C-reactive protein levels. Circulation 2001; 103: 1933-5.
8. Rosenson R. Statins in atgerosclerosis: lipid-lowering agents with antioxidant capabilities. Atherosclerosis. 2004; 173:1-12.

9. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Mac Farlane PW, Mc Killop JH, Packard CJ, for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men hypercholesterolemia. N Engl J Med 1995; 333: 1301-1307.
10. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS[Air Force/ Texas Coronary Atherosclerosis Prevention Study]. JAMA 1998; 279: 1615-1622.
11. Sever PS, Dahlof B, Poulter NR, Dahlof B, Wedel H, Collings R, Beevers G, Caufield M, Kjeldsen SE, Kristinsson A. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations in the Anglo-Scandinavian Cardiac Outcome Trial-Lipid Lowering Arm (ASCOT-LLA): a multicenter randomized controlled trial. Lancet 2003; 361: 1149-1158.
12. Scandinavian Simvastatin Survival Study Writing Group Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994: 344: 1383-1389.
13. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E, for the Cholesterol and Recurrent Events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996; 335: 1001-1009.
14. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339: 1349-1357.

15. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002; 360: 7-22.
16. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. Lancet 2002; 360: 1623-1630.
17. Pazzucconi F, Dorigotti F, Gianfranceschi G, Campagnoli G, Sirtori M, Franceschini G, Sirtori CR. Therapy with HMG-CoA reductase inhibitors: characteristics of the long term permanence of hypocholesterolemic activity. Atherosclerosis 1995; 117: 189-98.
18. Chasman D, Posada D, Subrahmanyan L, Cook N, Stanton V and Ridker P. Pharmacogenetics Study of Statin Therapy and cholesterol reduction. JAMA 2004; 291: 2821-2827.
19. Thompson JF, Man M, Johnson KJ, Wood LS, Lira ME, Lloyd DB. An association study of 43 SNPs in 16 candidate genes with atorvastatin response. Pharmacogenomic J. 2005; 5: 352-358.
20. Tong Y, Zhang S, Li H, Su Z, Kong X, Liu H, Xiao C, Sun Y, Shi JJ. 8302A/C and (TTA)n polymorphisms in the HMG-CoA reductase gene may be associated with some plasma lipid metabolic phenotypes in patients with coronary heart disease. Lipid 2004; 39: 239-241.
21. Hubacek JA, Pistulkova H, Valenta Z, Poledne R. (TTA)n repeat polymorphism in the HMG-CoA reductase gene and cholesterolaemia. Vasa 1999; 28: 169-171.
22. Plat J and Mensink RP. Relationship of genetic variation in genes ecoding apolipoprotein A-IV, scavenger receptor BI, HMG-CoA reductase, CETP and apolipoprotein E with cholesterol metabolism and the response to plant stanol ester consumption. Eur J Clin Invest 2002; 32: 242-250.

23. Rifai N, Tracy RP, Ridker PM. Clinical efficacy of an automated high-sensitivity C-reactive protein assay. Clin Chem 1999; 45: 2136-2141.

24. Pradelles P, Grassi J, Maclouf J. Enzyme immunoassays of eicosanoids using AchE as label: An alternative to radioimmunoassay. Anal Chem 1985; 57: 1170-1173.

25. Friedewald WT, Levy RI, Fredrickson DS. Estimation of low-density lipoprotein cholesterol without the use of the preparative ultracentrifuge. Clin Chem 1972; 18: 499-502.

26. Lalovic A, Sequeira A, DeGuzman R, Chawky N, Lesege A, Seguin M, Turecki G. Investigation of completed suicide and genes involved in cholesterol metabolism. J Affect Disord 2004; 79: 25-32.

27. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. Circulation 2004: 109: Suppl 1: III-39-III-43.

Table I. Baseline characteristics of recruited patients with CAD distributed according to the HMGCT (TTA)n repeat polymorphism (n=64)

	(TTA) >10/>10 (n=22)	(TTA) >10/10 (n=14)	(TTA) 10/10 (n=28)	P value
Age (years)	64 ± 8	65 ± 9	66 ± 8	0.796¥
Men	16 (73%)	12 (86%)	23 (82%)	0.668§
Body mass index (Kg/mt^2)	29 ± 5	26 ± 4	28 ± 3	0.227¥
Cardiovascular risk factors				
Hypertension	21 (95%)	13 (93%)	27 (96%)	0.875§
Diabetes mellitus	5 (23%)	3 (21%)	9 (32%)	0.762§
Dyslipidemia	22(100%)	14(100%)	28(100%)	
Smoking	3 (14%)	4 (29%)	1 (4%)	0.070§
Family history of CAD	8 (36%)	4 (29%)	17 (61%)	0.114§
Etiology				
Previous myocardial infarction	11 (50%)	9 (64%)	14 (50%)	0.691§
Previous coronary bypass surgery	17 (77%)	8 (57%)	23 (82%)	0.242§
Previous PTCA	9 (41%)	9 (64%)	10 (36%)	0.228§
Previous cerebrovascular accident	2 (9%)	2 (14%)	3 (11%)	0.886§
Vascular disease	3 (14%)	6 (43%)	2 (7%)	0.102§
Stable angina	6 (27%)	4 (29%)	9 (32%)	0.939§
Unstable angina	7 (32%)	7 (50%)	12 (43%)	0.529#
Chronic therapy				
ACE inhibitors	13 (59%)	9 (64%)	14 (50%)	0.649§
Angiotensin receptor antagonists	1 (5%)	1 (7%)	5 (18%)	0.353§
β-blockers	15 (68%)	7 (50%)	17 (61%)	0.552#
Diuretics	5 (23%)	2 (14%)	11 (39%)	0.216§
Calcium antagonists	5 (23%)	2 (14%)	2 (7%)	0.335§
Aspirin	11 (50%)	13 (93%)	26 (93%)	0.235§
Laboratory				
Total cholesterol (mg/dL)	207 ±29	229 ± 39	213 ± 37	0.173¥
LDL cholesterol (mg/dL)	134 ± 23	141 ± 30	137 ± 34	0.793*
HDL cholesterol (mg/dL)	41 ± 9	49 ± 17	41 ± 10	0.342*
Triglycerides (mg/dL)	158 ± 63	183 ± 69	175 ± 86	0.645*
hsCRP (mg/L), (range)	2.6 (0.4 - 20.3)	1.2 (0.1 - 6.9)	2.1 (0.1 - 14.1)	0.267*
F2-isoprostane (pg/mL)	44.2 ± 20	53.1 ± 19	48.9 ± 23	0.317*

Values are means ± SD, numbers of patients (porcentages), or medians (ranges).

CAD: coronary artery disease.

hsCRP: high-sensitivity C-reactive protein

PTCA: Previous percutaneous coronary angioplasty

¥ ANOVA (Analysis of Variance) * Kruskal-Wallis rank test. § Fisher's exact test. #Chi-square test

TABLE II. Genotype distribution and allele frequency the (TTA)n polymorphism in the HMGCR gene from CAD patients.

	(TTA) >10/>10 n (%)	(TTA) >10/10 n (%)	(TTA) 10/10 n (%)
Total CAD patients	22 (34)	14 (22)	28 (44)

CAD: coronary artery disease.

TABLE III. Effect of 8 week treatment with atorvastatin and HMGCR (TTA)n polymorphism on cholesterol, triglycerides, hsCRP and F-2 isoprostane in patients with CAD.

	(TTA) >10/>10 (n=22)	(TTA) >10/10 (n=14)	(TTA) 10/10 (n=28)	P value*
Total cholesterol (mg/dL), (%)	-74 ± 29 (-35.1)	-74 ± 28 (-32.3)	-73 ± 28 (-33.7)	0.117
LDL cholesterol (mg/dL), (%)	-63 ± 22 (-46.1)	-65 ± 25 (-45.6)	-61 ± 24 (-44.5)	0.743
HDL cholesterol (mg/dL), (%)	-0.7 ± 7 (-1.4)	-3 ± 8 (-5.0)	0.7 ± 6 (2.0)	0.292
Triglycerides (mg/dL), (%)	-53 ± 55 (-27.0)	-37 ± 60 (-20.3)	-60 ± 71 (-28.7)	0.667
hsCRP (mg/L), median (range)	-1.2 ± 6.4	-0.3 ± 2.4	-0.9 ± 3.9	0.406
	0.8 (-18.2 to 19.0)	0.2 (-2.3 to 6.6)	0.5 (-11.5 to 12.5)	
F-2 isoprostane (pg/mL), (%)	-21 ± 18 (-41.9)	-23 ± 21 (-38.2)	-25 ± 25 (-44.9)	0.542

Values are mean of change ± SD. For hsCRP is also displayed median (range)

hsCRP: high-sensitivity C-reactive protein

* Kruskal-Wallis test.

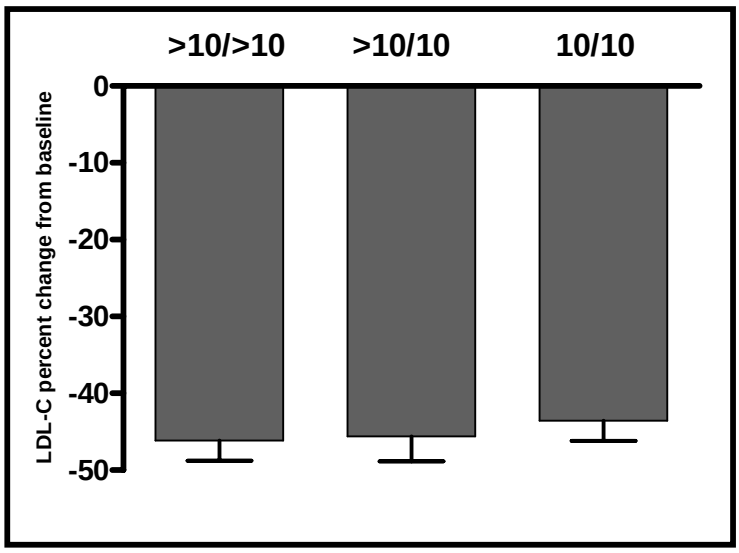

Figure 1. Percent change from baseline in LDL cholesterol for different (TTA)n polymorphism at 8 weeks treatment with atorvastatin; p= 0.743. >10/>10 polymorphism had two alleles with more than 10 TTA repeats, >10/10 one allele and 10/10 had two alleles with 10 TTA repeats.

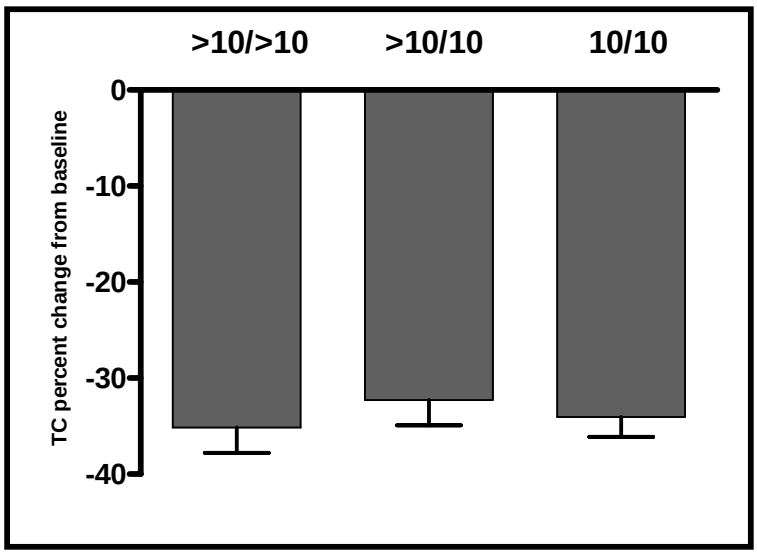

Figure 2. Percent change from baseline in total cholesterol (TC) for different (TTA)n polymorphism at 8 weeks treatment with atorvastatin; p= 0.117. >10/>10 polymorphism had two alleles with more than 10 TTA repeats, >10/10 one allele and 10/10 had two alleles with 10 TTA repeats.