Published in final edited form as:

J Mol Med (Berl). 2002 November ; 80(11): 737–744. doi:10.1007/s00109-002-0381-z.

Effects of SREBF-1a and SCAP polymorphisms on plasma levels of lipids, severity, progression and regression of coronary atherosclerosis and response to therapy with fluvastatin

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Abstract

Sterol regulatory elements binding factor-1a (SREBF-1a) and SREBF cleavage activating protein (SCAP) regulate lipids homeostasis. Polymorphisms in *SREBF-1a* and *SCAP* could affect plasma levels of lipids and risk of atherosclerosis. We determined association of *SREBF-1a* -36del/G and *SCAP* 2386A/G genotypes with plasma levels of lipids, severity and progression/regression of coronary atherosclerosis, and response to treatment with fluvastatin in a well-characterized Lipoprotein Coronary Atherosclerosis Study population. Plasma lipids and quantitative indices of coronary atherosclerosis were obtained at baseline and 2.5 years following randomization to fluvastatin or placebo in 372 subjects. Fluvastatin reduced plasma levels of total cholesterol by 16%, LDL-C by 25%, and ApoB by 16% and increased plasma levels of HDL-C by 9% and apoA-1 by 7%. Distributions of *SREBF-1a* *SCAP* genotypes were 60 GG, 172 del-G and 140 del-del and 88 GG, 188 GA and 96 AA, respectively. There were no significant differences in baseline plasma levels of lipids or indices of severity of atherosclerosis among the genotypes of each gene. There was a strong graded genotype-treatment interaction between *SREBF-1a* genotypes and change in apoA-I levels in response to fluvastatin (16.5% increase in GG, 10.5% in del/G, and 0.4% in del/del groups). Modest interactions between *SREBF-1a* genotypes and changes in HDL-C, and apoC-III levels in response to fluvastatin were also present. No genotype-treatment interaction for progression or regression of coronary atherosclerosis was detected. There were no significant interactions between *SCAP* genotypes and response to therapy. Thus we detected a strong graded interaction between *SREBF-1a* -36del/G genotypes and response of plasma apoA-I to treatment with fluvastatin.

Keywords

Atherosclerosis; Polymorphism; Pharmacogenetics; SCAP; SREBP

Introduction

Sterol regulatory element binding factors or proteins (SREBFs or SREBPs) are members of the basic-loop-helix-leucine zipper transcription factors family that upon activation bind to sterol regulatory element (SRE) sites in the 5'-regulatory region of many genes and promote their expression [1,2]. In cells replete with sterol SREBFs are membrane bound and thus inactive. In sterol-depleted cells a "sterol sensor" protein referred to as SREBF cleavage activating protein (SCAP) binds tightly to the COOH-terminal regulatory domains of SREBFs and chaperones transport of SREBFs from the endoplasmic reticulum to the Golgi [3]. Subsequently a two-step cleavage of the NH₂-terminal domains results in release of active SREBFs, which translocate into nucleus, bind to SRE in the promoter region of the target genes and increase their transcription. Experimental studies suggest that the SCAP-SREBF pathway plays a fundamental role in regulating cholesterol metabolism [4,5,6,7]. The potential clinical significance of the SCAP-SREBF pathway is illustrated by the recent development of SCAP ligands that activate SREBFs and reduce plasma levels of lipids in hyperlipidemic hamsters [8].

In view of the significant role of SCAP-SREBF pathway in regulating lipid metabolism, we hypothesized single nucleotide polymorphisms (SNPs) in genes encoding SCAP and SREBFs could affect plasma levels of lipids, susceptibility to coronary atherosclerosis, and response to treatment with lipid lowering agents (pharmacogenetics). Thus we determined association of the -36del-G SNP in *SREBF1a* and Ile796Val (2386A/G) SNP in *SCAP* with plasma levels of lipids and severity and progression/regression of coronary atherosclerosis in a prospective study in a well-characterized population. In addition, we determined association of the SNPs with changes in plasma levels of lipids and indices of severity of coronary atherosclerosis in response to treatment with fluvastatin.

Materials and methods

Study population

All subjects signed informed consents and the institutional review board approved the study. The design and primary results of the Lipoprotein and Coronary Atherosclerosis Study (LCAS) have been published [9,10]. In brief, 429 subjects who were 35–75 years of age and had a low-density lipoprotein cholesterol (LDL-C) level of 115–190 mg/dl despite diet and at least one coronary lesion causing 30–75% diameter stenosis were randomized to fluvastatin (40 mg daily) or placebo. Total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglyceride, apolipoproteins (Apo), and lipoprotein(a) levels were measured in all subjects and quantitative coronary angiography was performed at baseline ($n=340$) and 2.5 years after randomization ($n=316$). Clinical events monitored were definite or probable myocardial infarction, unstable angina requiring hospitalization, percutaneous coronary interventions, coronary artery bypass grafting, and death of any cause.

Genotyping of -36del/G SNP in *SREBF-1a* and 2386A/G (Ile796Val) SNP in *SCAP*

Genotyping for the -36del/G and 2386G/A SNPs were performed by PCR and restriction mapping with *ApaI* [11] and *MspI* [12] restriction enzymes, respectively, as published. An investigator with no knowledge of the angiographic and clinical data performed the genotyping. Accuracy of genotyping was determined by sequencing of the amplified fragment in 75 subjects including 50 subjects who were heterozygous according to restriction mapping technique.

Statistical analysis

Continuous variables are expressed as mean $\pm$ SD. Differences between the genotypes were compared by analysis of variance for phenotypes with equal variance and by Kruskal-Wallis test for those with unequal variance. Differences between the placebo and treatment groups were compared using Student's *t* test. Distribution of the categorical variables among genotypes was compared using Pearson's χ^2 or Fisher's exact test. To detect interactions between the genotypes and response to treatment mean changes in plasma lipid levels and minimal lumen diameter (MLD) between the genotypes were compared using analysis of variance (general linear model).

Results

Effects of fluvastatin on biochemical, angiographic and clinical phenotypes in the genetic subpopulation

The results in 372 subjects for whom DNA was available were similar to those observed in the entire LCAS population [9]. Overall, treatment with fluvastatin reduced plasma levels of total cholesterol, LDL-C, and apoB and increased plasma levels of HDL-C and apoA-I significantly (Table 1). Similarly, treatment with fluvastatin slowed progression and enhanced regression of coronary atherosclerosis in the genetic subpopulation (Table 1).

SREBF-1a –36del/G genotypes

The size of the PCR product was 213 bp. Deletion of a G nucleotide at position –36 abolishes a restriction site for *Apal* enzyme. Subjects with GG genotype were identified by the presence of 127 and 86-bp products, heterozygous subjects (del-G) by the presence of 212 bp, 127- and 86-bp products, and those homozygous for the deletion (del-del) by the presence of 212-bp product on agarose gel electrophoresis. The accuracy of genotyping was confirmed in 74/75 subjects by direct sequencing and one subject who had GG by restriction mapping had del-G genotype upon sequencing. Genotyping was completed in 372 subjects in the LCAS population (DNA was not available in 55 subjects). Distribution of the genotypes was 60 GG, 172 del-G and 140 del-del. The frequency of the G allele was 0.6.

SCAP 2386A/G (I796 V) genotypes

Genotyping was completed in 372 subjects. The size of the PCR product was 235 bp. Presence of G nucleotide abolishes an *MspI* restriction site. Therefore subjects with GG genotype (*n*=88) were identified by the presence of a 235-bp product, those with GA (*n*=188) by 235-, 158-, and 77-bp products, and those with AA (*n*=96) by the presence of 158- and 77-bp products on agarose gel electrophoresis. The frequency of the G allele was 0.49. Accuracy of genotyping was confirmed in 50 subjects by direct sequencing.

Genotypes and demographic and clinical phenotypes

Demographic and clinical characteristics, such as age, gender, ethnic background, height, weight, body mass index, systolic and diastolic blood pressure, waist/hip ratio, history smoking, and history of myocardial infarction are shown in Table 2. The most significant difference was in the distribution of the *SREBF-1a* genotypes between whites and African-Americans. Of the 26 African-Americans in the study population 9 had del-G and 17 had del-del genotypes (*df*=2, χ^2 =53.5, *P*<0.001, compared to distribution of the genotypes in whites). Therefore association of the *SREBF-1a* genotypes with biochemical, angiographic, and clinical phenotypes was analyzed in whites only.

Genotypes and baseline plasma levels of lipids and indices of severity of coronary atherosclerosis

The results are shown in Table 2. There were no significant differences in plasma levels of lipids between genotypes of each gene. There was also no significant association between the *SREBF-1a* and *SCAP* genotypes and indices of severity of coronary atherosclerosis, such as average MLD and the number of qualifying coronary lesions, as shown in Table 2. Subgroup analyses performed according to ethnic background, gender, age less than 60 years, presence or absence of diabetes mellitus, and smoking did not show an association between the genotypes and the baseline severity of coronary atherosclerosis.

Genotypes and natural progression/regression of coronary atherosclerosis

Changes in mean MLD, number of new coronary lesions, and number of total occlusions and the number of subjects who showed progression, a mixed pattern, or regression of coronary atherosclerosis during the course of 2.5 years' follow-up in the placebo group were not significantly different between the genotypes (Tables 3, 4). Subgroup analysis according to variables listed above also did not show a significant association between the genotypes and indices of progression or regression of coronary atherosclerosis.

Genotypes and response to therapy (pharmacogenetics)

There was a strong genotype-treatment interaction between *SREBF-1a* -36del-G genotypes and response of plasma levels of apoA-I and apoC-III to treatment with fluvastatin (Table 3). Probability plots of change in apoA-I according to genotypes are shown in Fig. 1. Subjects homozygous for the G allele had the greatest response (16.5% increase), those heterozygous had an intermediary response (10.5% increase), and those homozygous for the deletion allele had no changes in the plasma levels of apoA-I ($df=2$, $F=8.6$, $P=0.001$). Similarly, those with the GG genotype had had the largest increase in apoC-III ($P=0.05$). There was a modest interaction between *SREBF-1a* -36del-G genotypes and response of HDL-C to treatment ($P=0.086$). There were no significant interactions between the genotypes and the response of other lipids or angiographic indices of progression or regression of coronary atherosclerosis to treatment with fluvastatin. Subgroup analysis in categories cited above did not change the results, and the association of *SREBF-1a* genotypes with response of apoA-I to treatment with fluvastatin remained highly significant. Men with del-del genotype had 0.0% change in plasma levels of apoA-I, those heterozygous had 10.5% increase, and those with GG genotype had a 16.5% increase ($df=2$, $F=7.2$, $P=0.001$). No significant interactions between the genotypes and response to therapy were detected in women and nonwhite subjects. However, the numbers of women and nonwhites in this study were small. There were no significant interactions between *SCAP* genotype and response to therapy.

Genotypes and clinical events

Morbid or fatal events occurred in 55 patients (15%). The distribution of clinical events between the genotypes in the placebo and fluvastatin groups was not significantly different (Tables 3 and 4).

Discussion

LCAS is a prospective randomized study designed to assess effects of fluvastatin on plasma levels of lipids and progression/regression of coronary atherosclerosis [9,10]. Prospective design and extensive phenotypic characterization of the LCAS population provide an excellent opportunity to determine the genetic basis of interindividual variability in response to lipid lowering agents (pharmacogenetics) not only with regard to variability in plasma

levels of lipids but also with regard to progression and regression of coronary atherosclerosis. The LCAS population also provides an opportunity to determine the effects of the candidate SNPs on baseline plasma levels of lipids, severity of coronary atherosclerosis, and the natural progression of coronary atherosclerosis [13,14,15,16]. In this study we determined association of two SNPs in *SREBF-1a* and *SCAP* with biochemical, angiographic, and clinical phenotypes in the LCAS population. Overall, treatment with fluvastatin reduced plasma levels of total cholesterol, LDL-C, and apoB, increased plasma levels of HDL-C and apoA-I and slowed progression, and enhanced regression of coronary atherosclerosis in the genetic subpopulation. The interesting observations in the present study were the presence of a strong graded genotype-treatment interaction between -36del/G genotypes and plasma levels of apoA-I and apoC-III and to a modest degree between -36del/G genotypes and HDL-C. The effect was gene-dose dependent, and homozygosity for the deletion allele completely abolished the response of plasma apoA-I to treatment with fluvastatin. Despite significant changes in the plasma levels of apoA-I and apoC-III there was no significant genotype-treatment interaction with regard to progression or regression of coronary atherosclerosis. This finding illustrates that it is more likely to find an association with an immediate phenotype that is directly related to function of the gene than with a distant phenotype, which is affected by numerous additional factors.

The mechanism(s) of the observed interactions between -36del/G genotypes in *SREBF-1a* and response of plasma levels of apoA-I and apoC-III to treatment with fluvastatin is likely to involve differential effects of the alleles on multiple target genes involved in lipoprotein metabolism. While SREBFs were initially identified as transcription factors that regulate expression of LDL receptors [17], it is now recognized that SREBFs affect expression of a diverse array of genes by binding to multiple sites including SRE (CACCCAC) and E-box type (CANNTG) palindromic sequences on the 5' regulatory regions of genes. The primary targets for SREBFs are genes encoding for enzymes involved in lipid metabolism, such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase [18], apoA-II [19], lipoprotein lipase [20], cholesteryl ester transfer protein [20], microsomal triglycerides transfer protein [21], farnesyl diphosphate synthase [22], fatty acid synthase [23], and squalene [24], among many others [25]. Polymorphisms that affect expression levels or structure of active domains of SREBF-1a could affect transcription of *APOA1* gene and plasma levels of apoA-I. The mechanism of the observed genotype-treatment interactions is further compounded by the direct effects of fluvastatin on transcription of several SREBFs-responsive genes, such as HMG-CoA synthetase, HMG-Co A reductase, and farnesyl-pyrophosphate synthase [26]. In addition to the biological plausibility of the observed genotype-treatment interaction, strength of the association and the presence of gene-dose effect favor a true association. Nevertheless, the results are considered provisional pending proof through experimentation.

The possibility of an α error also exists because of multiple analyses, which were performed assuming full independence of each hypothesis. The assumption of independence of phenotypes was made because transcriptional regulation of lipid related genes (e.g., *APOA1*, *APOB*), by SREBF1a or other transcriptional factors is not considered fully dependent. Similarly, genotype-treatment interaction for each variable is considered largely unrelated processes. According to Tukey [27], it is mandatory to adjust the significance level for multiple hypotheses only when the hypotheses being tested are not fully independent of one another. It is noted that the observed *P* value for genotype-treatment interaction for changes in apoA-I remains significant after corrections for five levels of multiple comparisons. Nevertheless, because of multiple testing, the significant *p* values ($P < 0.05$) should be regarded as potential associations and the observed interactions hypothesis generating results. It is also noted that the choice of end points, duration of the study, and the inclusion criteria were determined prior to genetic analysis. Therefore genetic studies of LCAS

population are considered secondary data analysis. Furthermore, the observed interaction between the -36del-G genotypes and response to fluvastatin require confirmation in additional independent studies.

We found no significant association between *SREBF-1a* and *SCAP* genotypes and baseline plasma levels of lipids or the severity of coronary atherosclerosis. A previous study showed a modest association between *SREBF-1a* -36del/G genotypes and plasma levels of LDL-C in a French population [11]. The lack of an association in the present study may reflect population characteristics of the two studies including the prevalence of conventional risk factors. For example, the prevalence of diabetes mellitus ($n=14$, 4%) and smoking ($n=75$, 20%) was relatively low, and the mean LDL-C level was 144.6 ± 20.0 mg/dl in the LCAS genetic subpopulation ($n=372$). With regard to the possibility of β error, the sample size of this study provided greater than 95% power to detect a 10% difference in the baseline values of mean plasma levels of LDL-C (15 mg/dl) and apoB (13.5 mg/dl) among the genotypes. The study also had a minimum of 80% power to detect 0.17- and 0.20-mm differences in the baseline values of mean MLD among the genotypes of *SCAP* and *SREBF-1a*, respectively. The study had at least 80% power to detect 11 mg/dl differences in $\Delta\text{LDL-C}$ among the genotypes and 0.29 mm differences in mean ΔMLD in response to fluvastatin. We note that the mean MLD in the placebo and fluvastatin groups decreased only by -0.11 and -0.04 mm, respectively, during 2.5 years of follow-up. Thus it could be inferred that the study, in particular the subgroup analysis, had insufficient power to detect modest differences in the mean MLD among the genotypes. Similarly, smaller genotype-treatment interactions with regard to changes in mean plasma levels of LDL-C and mean MLD could not be detected. In addition, the duration of LCAS (2.5 years) was relatively short, and the number of new clinical events was low (55 events), which may not be sufficient to detect possible genotype-treatment interactions or association of the genotypes with clinical events or progression/regression of coronary atherosclerosis. Overall, there were no genetic or biological gradients or a trend toward an association with multiple dependent phenotypes to suggest the possibility of type β error. Furthermore, a recent study performed in 51 men did not find a significant interaction between *SCAP* 2376A/G genotypes and response to treatment with fluvastatin [28].

In summary, we showed a strong gene-dose dependent interaction between the -36del/G *SREBF-1a* genotypes and response of plasma levels of apoA-I and apoC-III to treatment with fluvastatin. A modest interaction between *SREBF-1a* genotypes and with response of HDL-C to fluvastatin was also observed. We conclude that -36del/G genotypes of *SREBF-1a* is associated with the response of plasma lipids to treatment with fluvastatin in the LCAS population, representative of a population with mildly to moderately elevated LDL-C, who underwent cardiac catheterization.

Acknowledgments

Funding for LCAS was provided by Novartis Pharmaceuticals Corporation grant no. B351 and National Institutes of Health GCRC grant no. 5M01RR00350. This work was also supported in part by a grant from Nijad Fares and Jeff Hines. C.M. Ballantyne and A.J. Marian are recipients of Established Investigator Awards from the American Heart Association National Center, Dallas, Texas.

Biographies

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A.J. MARIAN received his training in clinical and molecular cardiology in the American Heart Association-Bugher Foundation Fellowship program at Baylor College of Medicine, Houston, Texas. He is currently an Associate Professor of Medicine at Baylor College of Medicine and an Associate Editor of *Circulation*. His areas of research are molecular genetics of cardiovascular disease.

Abbreviations

<i>Apo</i>	Apolipoproteins
<i>ApoB</i>	Apolipoprotein B
<i>HMG-CoA</i>	3-Hydroxy-3-methyl-glutaryl coenzyme A
<i>LCAS</i>	Lipoprotein and Coronary Atherosclerosis Study
<i>LDL-C</i>	Low-density lipoprotein cholesterol
<i>MLD</i>	Minimal lumen diameter
<i>SCAP</i>	SREBF cleavage activating protein
<i>SNP</i>	Single nucleotide polymorphisms
<i>SRE</i>	Sterol regulatory element
<i>SREBF</i>	Sterol regulatory elements binding factor

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Fig. 1.
Probability plots of percent changes in apoA-I according to $-36\text{del}/\text{G}$ genotypes of SREBF1a

Table 1

Effects of fluvastatin on plasma lipids, severity of coronary atherosclerosis and clinical events (*TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglyceride, *ApoA-I* apolipoprotein A-I, *ApoB* apolipoprotein B, *ApoC-III* apolipoprotein C-III, *Lp(a)* lipoprotein(a), *MLD* minimum lumen diameter, *SNP* single nucleotide polymorphism)

	Placebo	Fluvastatin	P
Lipids			
<i>n</i> =372	181	191	
ΔTC (%)	-1.1±13	-16.0±13	<0.001
ΔHDL-C (%)	3.6±15	9.3±15.7	<0.001
ΔLDL-C (%)	-4.2±17.5	-25.3±17.5	<0.001
ΔTG (%)	9.8±40.2	0.8±40.8	0.033
ΔApoA-1 (%)	1.3±15.0	6.9±20.1	0.005
ΔApoB (%)	5.2±20.2	-16.0±15.4	<0.001
Angiographic indices			
<i>n</i> =316	154	162	
No. of new lesions	0.36±0.48	0.26±0.44	0.060
No. of new occlusion	0.07±0.26	0.03±0.17	0.10
Categorical progression/regression			0.036
Progression (%)	61 (40%)	47 (29%)	
Regression (%)	12 (8%)	24 (15%)	
Mixed (%)	81 (52%)	90 (56%)	
Δ MLD (mm)	-0.11±0.24	-0.04±0.25	0.008
Clinical events			
<i>n</i> =55/372 (15%)	30 (17%)	25 (13%)	0.3

SREBF-1a -36del/G and *SCAP* I796 V genotypes and baseline demographics, plasma lipids, and severity of coronary atherosclerosis (*BMI* body mass index, *BP* blood pressure, *TC* total cholesterol, *Lp(a)* lipoprotein(a), *qual* qualifying lesions)

Table 2

	Entire population (n=372)	SREBF-1a -36del/G			SCAP 2386A/G (I796 V)		
		del-del 140	del-G 172	GG 60	AA (II) 96	AG (IV) 188	GG (VV) 88
Demographics							
Age (years)	58.8±7.7	58.6±7.8	59.5±7.7	56.8±7.8*	58.9±8.4	58.8±7.75	58.6±7.85
Male	310 (83%)	117 (84%)	143 (84%)	50 (81%)	83 (86%)	147 (78%)	80 (91%)*
White	333 (90%)	137 (98%)	154 (89%)	42 (70%)*	91 (95%)	167 (89%)	75 (95%)
Height (m)	1.73±0.08	1.74±0.08	1.73±0.08	1.74±0.09	1.73±0.08	1.73±0.08	1.75±0.08
Weight (kg)	84.5±15.4	85.4±17.1	83.9±15.8	84.3±12.5	85.6±15.9	82.2±14.3	88.2±16.5*
BMI	28.1±4.4	28.1±5.0	28.1±4.3	27.9±3.3	28.4±4.5	27.5±4.1	28.8±4.7*
Waist/hip ratio	0.91±0.07	0.91±0.06	0.90±0.07	0.91±0.06	0.91±0.07	0.90±0.07	0.92±0.07
Systolic BP (mmHg)	124.4±15.2	125.5±16.9	123.5±14.0	124.4±15.08	124.8±14.4	123.87±15.5	125.2±15.6
Diastolic BP (mmHg)	78.0±9.1	77.0±9.1	76.5±9.1	78.3±8.6	77.7±8.0	76.6±9.6	76.0±8.9
Previous MI	154 (41%)	61 (44%)	69 (41%)	24 (39%)	34 (35%)	80 (43%)	40 (45%)
Diabetes mellitus	14 (4%)	6 (4%)	4 (2%)	4 (8%)	3 (3%)	9 (5%)	2 (2%)
Smoker	75 (20%)	31 (22%)	37 (22%)	7 (11%)	22 (23%)	35 (19%)	18 (20%)
Lipids							
TC (mg/dl)	221.7±27.1	219.6±26.7	223.7±28.8	220.9±22.9	223.1±25.0	221.1±27.5	221.2±28.7
HDL-C (mg/dl)	43.9±11.5	42.9±12.0	44.3±11.5	44.3±11.1	43.4±9.2	44.3±12.3	43.6±12.2
LDL-C (mg/dl)	145.2±22.9	143.3±21.9	146.8±21.7	144.4±20.8	143.3±21.9	146.9±24.5	144.7±20.8
TG (mg/dl)	163.7±63.1	164.2±64.0	165.0±62.0	168.7±63.6	168.6±60.5	164.9±62.9	155.8±65.8
ApoA-I (mg/dl)	133.0±7.3	131.2±27.5	134.2±27.9	132.4±25.6	133.9±23.6	132.3±27.6	131.6±30.3
ApoB (mg/dl%)	134.9±20.9	133.5±20.7	135.3±21.6	136.1±20.0	137.34±19.0	133.3±21.7	135.8±21.0
ApoC-III (mg/dl)	37.0±12.1	36.8±11.7	37.6±12.9	36.1±10.5	37.8±12.0	37.5±11.4	35.2±13.6
Lp(a) (mg/dl)	37.2±33.8	36.5±34.7	35.7±32.1	42.6±36.3	37.1±32.8	38.09±35.2	35.4±32.0
Angiographic indices							
n (per SNP)	316	122	142	52	82	164	70
No. of qual lesions	3.0±1.4	3.01±1.4	3.05±1.4	2.81±1.4	2.87±1.5	3.1±1.4	3.0±1.3
No. of occlusions	0.32±0.59	0.27±0.53	0.36±0.61	0.33±0.63	0.34±0.58	0.34±0.63	0.26±0.49

	Entire population (n=372)	SREBF-1a -36del/G			SCAP 2386A/G (1796 V)			
		del-del 140	del-G 172	GG 60	AA (II) 96	AG (IV) 188	GG (VV) 88	
≥ one qual lesion	262 (80%)	101 (83%)	120 (85%)	41 (80%)	65 (80%)	138 (84%)	59 (84%)	
≥ one occlusion	97 (25%)	31 (25%)	50 (29%)	16 (26%)	28 (29%)	48 (26%)	21 (24%)	
Mean MLD (mm)	1.67±0.40	1.69±0.39	1.64±0.40	1.79±0.46	1.64±0.37	1.67±0.42	1.73±0.42	

The *p* values represent the differences between the three genotypes; the location of symbols indicate whether the differences were in the placebo or in the treatment group

* *P*=0.056,
 ** *P*=0.02,
 *** *P*<0.001,
 4* *P*=0.008,
 5* *P*=0.05.

Table 3

SREBF-1a -36del/G genotypes, progression of coronary atherosclerosis and response to treatment with fluvastatin (*TC* total cholesterol, *LDL-C* low-density lipoprotein -cholesterol, *HDL-C* high -density lipoprotein -cholesterol, *TG* triglyceride, *ApoA-I* apolipoprotein A-I, *ApoB* apolipoprotein B, *ApoC-III* apolipoprotein C-III, *Lp(a)* lipoprotein(a), *MLD* minimum lumen diameter)

	Placebo		Fluvastatin			
	del-del	del-G	GG	del-del	del-G	GG
Lipids						
n=333 (whites)	62	78	24	75	76	18
ΔTC (%)	-2.2 $\pm$ 12.4	1.4 $\pm$ 12.2	-6.0 $\pm$ 14.8*	-16.5 $\pm$ 12.0	-15.6 $\pm$ 13.9	-13.0 $\pm$ 12.6
$\Delta HDL-C$ (%)	5.6 $\pm$ 16.4	2.4 $\pm$ 14.6	0.7 $\pm$ 14.9	8.0 $\pm$ 15.3	9.9 $\pm$ 14.9	12.9 $\pm$ 18.6
$\Delta LDL-C$ (%)	-6.0 $\pm$ 16.2	-1.3 $\pm$ 17.0	-9.5 $\pm$ 18.8**	-27.1 $\pm$ 16.1	-24.4 $\pm$ 19.2	-23.4 $\pm$ 20.0
ΔTG (%)	9.6 $\pm$ 41.6	12.7 $\pm$ 41.4	7.5 $\pm$ 40.7	1.7 $\pm$ 45.8	-3.6 $\pm$ 30.4	0.10 $\pm$ 25.2
$\Delta ApoA-I$ (%)	2.6 $\pm$ 13.2	1.7 $\pm$ 16.1	-4.3 $\pm$ 13.5	0.4 $\pm$ 16.8	10.5 $\pm$ 20.0	16.5 $\pm$ 22.9 ^{4*}
$\Delta ApoB$ (%)	2.4 $\pm$ 18.9	9.6 $\pm$ 20.9	1.4 $\pm$ 17.5***	-16.1 $\pm$ 15.1	-17.0 $\pm$ 15.7	-14.2 $\pm$ 17.4
$\Delta ApoC-III$ (%)	3.9 $\pm$ 36.4	2.2 $\pm$ 32.3	-2.7 $\pm$ 29.4	-5.2 $\pm$ 31.92	-7.3 $\pm$ 23.2	9.5 $\pm$ 24.7 ^{5*}
$\Delta Lp(a)$ (%)	-2.1 $\pm$ 33.8	-6.9 $\pm$ 32.2	-9.5 $\pm$ 25.6	-1.8 $\pm$ 37.5	-5.0 $\pm$ 35.7	-6.0 $\pm$ 37.5
Angiographic indices						
n=289	54	67	20	67	64	17
No. of new lesions	0.33 $\pm$ 0.48	0.31 $\pm$ 0.47	0.50 $\pm$ 0.51	0.24 $\pm$ 0.43	0.25 $\pm$ 0.44	0.41 $\pm$ 0.51
No. of new occlusion	0.07 $\pm$ 0.26	0.05 $\pm$ 0.21	0.10 $\pm$ 0.31	0.04 $\pm$ 0.20	0.02 $\pm$ 0.13	0.06 $\pm$ 0.24
$\geq$ one new lesion	18 (33%)	21 (31%)	10 (50%)	16 (23%)	16 (25%)	7 (41%)
$\geq$ one new occlusion	4 (7%)	3 (5%)	2 (10%)	3 (5%)	1 (2%)	1 (6%)
Categorical progression, regression						
Progression	24 (44%)	24 (36%)	8 (40%)	25 (37%)	14 (22%)	3 (18%)
Regression	5 (9%)	6 (9%)	0 (0%)	10 (15%)	7 (11%)	4 (24%)
Mixed	25 (46%)	37 (55%)	12 (50%)	32 (48%)	43 (67%)	10 (59%)
ΔMLD (mm)	-0.13 $\pm$ 0.27	-0.08 $\pm$ 0.23	-0.13 $\pm$ 0.20	-0.04 $\pm$ 0.27	-0.03 $\pm$ 0.22	-0.06 $\pm$ 0.30
Clinical events						
n=55/372 (15%)	12 (19%)	12 (15%)	3 (13%)	10 (13%)	7 (9%)	4 (22%)

* $P=0.032$,

^{**}
^{**} $P=0.077$,

^{***} $P=0.035$ between genotypes in the placebo group:

^{4*} $P=0.001$,

^{5*} $P=0.05$ between genotypes in fluvastatin group

Table 4

SCAP 2386A/G genotypes and response of plasma lipids and coronary atherosclerosis to treatment with fluvastatin (TC total cholesterol, LDL-C low-density lipoprotein -cholesterol, HDL-C high -density lipoprotein -cholesterol, TG triglyceride, ApoA-I apolipoprotein A-I, ApoB apolipoprotein B, ApoC-III apolipoprotein C-III, Lp(a) lipoprotein(a), MLD minimum lumen diameter)

	Placebo			Fluvastatin		
	AA	AG	GG	AA	AG	GG
Lipids						
n=372	43	93	45	53	95	43
ΔTC (%)	-1.4±11.5	0.5±13.8	-4.2±12.2	-17.0±12.5	-15.5±12.6	-13.4±14.5
ΔHDL-C (%)	0.6±16.4	4.5±15.1	4.5±15.0	7.2±1.5	10.0±17.2	10.1±13.6
ΔLDL-C (%)	-3.2±13.7	-2.6±18.5	-8.5±18.4	-28.2±13.8	-25.5±17.0	-21.5±21.9
ΔTG (%)	9.2±44.0	10.6±38.3	8.6±41.2	0.10±43.0	0.5±40.0	1.1±40.8
ΔApoA-1 (%)	-2.1±17.0	2.5±15.0	1.8±13.0	2.4±18.7	9.3±22.0	7.4±16.8
ΔApoB (%)	2.2±19.0	7.7±21.9	2.6±16.7	-19.3±14.7	-14.4±16.2	-15.1±14.3
ΔApoC-III (%)	-4.0±34.6	2.6±30.8	7.1±36.3	-6.2±27.3	-0.6±29.5	-4.8±34.0
ΔLp(a) (%)	-11.2±37.5	-1.5±31.0	-3.6±30.0	-10.4±34.0	1.0±37.0	-1.3±36.7
Angiographic indices						
n=316	36	81	37	46	83	33
No. of new lesions	0.31±0.47	0.32±0.47	0.49±0.51	0.28±0.46	0.22±0.41	0.33±0.48
No. of new occlusion	0.00±0.00	0.07±0.26	0.13±0.34*	0.04±0.21	0.02±0.15	0.03±0.17
≥ one new lesion (%)	11 (31%)	26 (32%)	18 (49%)	13 (28%)	18 (22%)	11 (33%)
≥ one new occlusion (%)	0 (0%)	6 (7%)	5 (14%)**	2 (4%)	2 (2%)	1 (3%)
Categorical progression, regression						
Progression (%)	13 (36%)	33 (41%)	15 (41%)	6 (13%)	30 (36%)	11 (33%)
Regression (%)	4 (11%)	6 (7%)	2 (5%)	6 (13%)	13 (16%)	6 (18%)
Mixed (%)	19 (53%)	42 (52%)	20 (54%)	34 (74%)	40 (48%)	16 (48%)
Δ MLD (mm)	-0.04±0.22	-0.14±0.26	-0.13±0.22	-0.03±0.25	-0.02±0.26	-0.07±0.23
Clinical events						
n=55/372 (15%)	9 (21%)	14 (15%)	7 (16%)	9 (17%)	11 (12%)	5 (21%)

* $P=0.081$,

** $P=0.080$