Apolipoprotein-E polymorphism and response to pravastatin in men with coronary artery disease (REGRESS)

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Objectve — The influence of ApoE polymorphism on the efficacy of statins in lowering plasma lipids and lipoproteins and improving angiographic parameters was assessed.

Methods: ApoE genotypes were studied in a group (n = 815) of well-characterised male coronary artery disease (CAD) patients who participated in the lipid-lowering regression study 'Regression Growth Evaluation Statin Study (REGRESS)'.

Results — There was a significant interaction between treatment (placebo/pravastatin) and APOE genotype when lipid levels were considered, APOE2 + carriers exhibited the largest improvement of HDL levels (+ 0.15 mmol/l) and LDL/HDL ratios (-0.60) compared with APOE3 + (+ 0.06 mmol/l, -0.043, respectively) and APOE4 + carriers (+ 0.07 mmol/l, -0.040). In contrast, APOE2 + allele carriers had the least effect in terms of angiographic parameters, although the difference was not statistically significant.

Conclusions — The effects of statins in subjects with different ApoE genotypes were different with regard to the lipoprotein profile, but not with regard to angiographic parameters.
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Introduction

Apolipoproteins play an essential role in the binding, uptake, clearance and catabolism of lipoproteins. They have major effects on lipoprotein levels and thus on coronary artery disease (CAD) risk. Apolipoprotein-E (ApoE) is an important surface constituent of lipoproteins[1]. There are three common alleles of ApoE, ε2, ε3, and ε4, which encode three isoforms, ApoE2, ApoE3 and ApoE4, respectively[2]. The ε2 allele is associated with increased levels of ApoE and triglycerides and decreased levels of cholesterol, while the ε4 allele is associated with higher plasma total and LDL-cholesterol levels[3]. Lipoproteins carrying the E4 isoform are taken up with greater affinity than those with the common E3 isoform, which, in turn, are cleared more efficiently than those with the E2 isoform. An accelerated lipoprotein clearance by the liver leads to a down-regulation of hepatocyte LDL receptor synthesis and consequently to an increase in plasma LDL cholesterol[4]. It has been estimated that ApoE accounts for as much as 10% of the total variation in cholesterol levels in the population[3]. ApoE is therefore considered an important candidate gene for CAD risk. Subjects with the ε2 allele are thought to have the most beneficial ApoE isoform (in the absence of dysbetalipoproteinaemia), while ε4 carriers are hypothesised to have

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the highest CAD risk[3,5]. However, some studies have suggested that the ApoE polymorphism is not an independent risk factor for CAD[6].

There is also controversy with regard to the influence of the ApoE polymorphism on the efficacy of statins. Some studies suggest that statins reduce cholesterol levels to a lesser extent in individuals with the ApoE4 isoform[7-11]. This might be explained by the fact that ε4 carriers have lower HMG-CoA reductase activity[7]. Still other studies did not confirm these findings[12-15]. In a post-hoc analysis of the Scandinavian Simvastatin Survival Study (4S) subjects with the ε4 allele had nearly twice the risk of dying, compared to patients without an ε4 allele. Simvastatin treatment reduced the risk of mortality by 67% in ε4 carriers and by 34% in non-ε4 carriers[16]. This excess mortality in ε4 carriers could be abolished by treatment with simvastatin. In contrast, a cohort study in an elderly population revealed no differences in the effectiveness of statins for subjects with different ApoE genotypes[17].

The aim of this study was to assess whether the effects of statins with regard to either lipid profile or angiographic parameters were influenced by ApoE genotype.

Methods

The patients from the REGRESS trial included in this study have been described in detail elsewhere[18]. Briefly, a total of 815 male CAD subjects, taking part in the randomised placebo-controlled REGRESS trial were included. After a wash-out period of 6 weeks for bile acid sequestrants and 12 weeks for HMG-CoA reductase inhibitors, patients younger than 70 years of age with symptomatic CAD were randomised to pravastatin (fixed dose of 40 mg) or placebo. Each subject had to have at least one coronary artery with a stenosis of > 50% and a qualifying total cholesterol level (normal to moderately raised) between 4 to 8 mmol/l (155 - 310 mg/dl) and triglycerides < 4 mmol/l (350 mg/dl). Quantitative coronary angiograms (QCA's) were performed at baseline and after 2 years of treatment, as described earlier[18].

After stratification for genotype we compared the efficacy of pravastatin to placebo with regard to lipid profiles and angiographic parameters.

Blood samples were collected from patients after an overnight fast. Total serum cholesterol, HDL-cholesterol and triglycerides were measured by standard techniques. Total cholesterol was determined with an enzymatic kit (Boehringer Mannheim, Mannheim, Germany) and calibrated. HDL-cholesterol was measured after precipitation of apolipoprotein B (ApoB)-containing lipoproteins with a 4% tungstate solution and centrifugation[20]. Triglycerides were analysed enzymatically (Bayer/Technicon)[21]. LDL-cholesterol was calculated using the Friedewald formula[22].

DNA was extracted from leukocytes by a standard procedure and stored at 4°C. ApoE genotyping was performed with the agarose-based method, as described by Reymer et al.[23].

Allele frequencies were estimated using the gene-counting method. Differences in mean lipid levels between ApoE groups were evaluated by parametric (one-way analysis of variance) and nonparametric (Kruskal-Wallis) tests. For pairwise contrasts of ApoE groups, both Scheffe's method (parametric test) and the Mann-Whitney U/Wilcoxon rank sum (nonparametric) test were used. We distinguished three different ApoE genotype groups in the analyses: ApoE2 + (Apo ε2ε2 or Apo ε2ε3), ApoE3 (ApoE ε3ε3) and ApoE4 + (ApoE ε3ε4 or ApoE ε4ε4). ApoE ε2ε4 genotypes were omitted from analyses due to their low frequency.

Results

The ApoE genotype distributions were in Hardy-Weinberg equilibrium. The frequencies of ApoE alleles in CAD patients were 0.067 for ε2, 0.774 for ε3 and 0.159 for ε4.

Table 1 shows that ApoE2 + carriers had significantly lower mean values of total cholesterol (5.82 mmol/l) than ApoE3 allele carriers (6.07 mmol/l) and ApoE4 + allele carriers (6.05 mmol/l), respectively. Similar results were evident with LDL-cholesterol levels. ApoE4 + carriers had no higher total and LDL cholesterol levels than ApoE3 carriers. HDL-cholesterol was significantly lower in ApoE4 + carriers, 0.89 mmol/l versus 0.94 mmol/l. Mean triglyceride levels (ln transformed) were higher in ApoE2 + carriers than in the other groups. The LDL/HDL-cholesterol ratios (ln transformed) were significantly different among ApoE genotypes; this remained true after adjusting for age, BMI, smoking and alcohol intake (data not shown).

Angiographic parameters at baseline (table 1) showed no significant differences for the average mean segment diameter (MSD), the average minimum obstructive diameter (MOD), or the percentage stenosis or presence of 1-, 2- or 3-vessel disease among ApoE genotype groups.

The changes of lipid and lipoprotein levels upon pravastatin therapy are reported in table 2. Within the pravastatin group total cholesterol, LDL-cholesterol, HDL-cholesterol, and LDL/HDL ratio levels significantly changed in the expected directions. ApoE2 + carriers showed a significantly better response to treatment with pravastatin than ApoE4 + carriers. There was a significant interaction between treatment and ApoE genotype; ApoE2 + carriers exhibited the largest improvement of HDL-cholesterol levels (and LDL/HDL ratios). In contrast ApoE2 + allele carriers showed the least effect in terms of angiographic parameters although these differences were not statistically significant (table 2).

Table 1. – *Baseline lipid, lipoprotein levels, and angiographic parameters according to ApoE genotype.*

ApoE genotype	2+	3	4+	
	n = 88	n = 490	n = 219	P[b]
Total-c (mmol/l) [a]	5.82 (0.93)	6.07 (0.86)	6.05 (0.86)	0.044
LDL-c (mmol/l) [a]	4.03 (0.84)	4.36 (0.77)	4.32 (0.78)	0.002
HDL-cl (mmol/l) [a]	0.94 (0.23)	0.94 (0.23)	0.89 (0.22)	0.028
Triglycerides (mmol/l) [ac]	1.97 (0.79)	1.76 (0.75)	1.78 (0.76)	0.044
LDL/HDL ratio[ac]	4.61 (1.32)	4.89 (1.41)	5.02 (1.37)	0.002
MSD (mm)	2.72 (0.34)	2.73 (0.39)	2.74 (0.46)	0.90
MOD (mm)	1.74 (0.31)	1.77 (0.36)	1.76 (0.35)	0.71
%Stenosis (%)	35.1 (11.57)	35.0 (12.89)	35.7 (14.59)	0.82
CAD: n%:				
1 vessel	40 (46%)	206 (42%)	83 (38%) }	
2 vessels	25 (29%)	171 (35%)	79 (36%) }	0.59
3 vessels	22 (25%)	111 (23%)	56 (26%) }	

[a] = mean (SD); n = sample size; Values are ± standard deviation; LDL = low-density lipoprotein; HDL = high-density lipoprotein. [b] p value of one-way analysis of variance or chi-square test, where appropriate. [c] For triglycerides and LDL/HDL ratio the p-value is calculated with ln transformed variables. MSD = mean segment diameter, MOD = mean obstructive diameter, CAD = presence of coronary artery disease in 1-, 2- or 3- vessels.

Table 2. – *Changes in lipids and lipoprotein levels in placebo and pravastatin groups according to ApoE genotype.*

	Placebo ApoE genotype				Pravastatin ApoE genotype				
	2+	3	4+		2+	3	4+		
	n = 41	n = 242	n = 107	P*	n = 47	n = 248	n = 112	P[d]	P[e]
Total-c [a]	0.25	0.14	0.11	0.91	−1.24	−1.26	−1.08	0.04	0.11
	(0.81)	(0.61)	(0.69)		(0.88)	(0.73)	(0.69)		
LDL-c [a]	0.14	0.02	0.05	0.99	−1.31	−1.29	−1.14	0.004	0.13
	(0.64)	(0.56)	(0.63)		(0.75)	(0.68)	(0.64)		
HDL-c [a]	0.01	0.03	0.05	0.69	0.16	0.09	0.12	0.01	0.02
	(0.13)	(0.13)	(0.12)		(0.17)	(0.16)	(0.13)		
Triglycerides	0.12	0.11	0.04	0.33	−0.13	−0.06	−0.05	0.75	0.32
	(0.33)	(0.32)	(0.32)		(0.37)	(0.40)	(0.36)		
LDL/HDL ratio	0.03	−0.03	−0.04	0.41	−0.57	−0.46	−0.44	< 0.001	< 0.001
	(0.21)	(0.17)	(0.17)		(0.29)	(0.26)	(0.19)		
MSD loss[b]	0.14	0.08	0.14	0.06	0.08	0.07	0.05	0.54	0.08
	(0.19)	(0.18)	(0.27)		(0.17)	(0.19)	(0.19)		
MOD loss[c]	0.13	0.07	0.10	0.03	0.12	0.02	0.03	0.10	0.78
	(0.23)	(0.22)	(0.22)		(0.22)	(0.20)	(0.20)		

[a] mean ± 1 SD (mmol/l); [b] mean± 1 SD (mm); [c]: median ± 1 IQR (mm). [d] p value of (co)variance analysis with baseline values as covariate; [e] p value of the interaction between treatment (placebo/pravastatin) and ApoE genotype of the covariance model with baseline values as covariate.

Discussion and conclusion

Apo ε2 carriers exhibited the largest improvement in lipoprotein levels upon pravastatin treatment, compared to those having an Apo ε3 or an Apo ε4 allele. The efficacy of pravastatin on angiographic parameters was less pronounced in the ApoE2 + group, but these differences were not significant.

Several other studies reported similar results[7-11], while others found no differences in subjects with and without ApoE*4 [12-15]. Even though the efficacy of pravastatin on lipid levels was not as large in ApoE4 + carriers, the effect on the progression of coronary atherosclerosis was the same (or even larger) as in the other patients. As far as we know, no other studies have looked at angiographic parameters. Two studies, however, assessed cardiovascular disease and total mortality. In the Rotterdam study different ApoE genotypes did not modulate the effectiveness of statins towards cardiovascular endpoints or total mortality[17]. The 4S study did not reveal differences in terms of cardiovascular disease, while total mortality was even more reduced with statins in ε4 carriers compared with the other genotypes (although not statistically significant)[16]. Measuring lipid levels might not be the best way to evaluate the effects of statin therapy, since less response in terms of lipid levels does not seem to predict less effect on CAD events. This might be explained by a protective effect of statins which is unrelated to lowering of serum cholesterol[28-31].

In the Rotterdam Study, men with the ε4ε4 genotype were 3.18 times more likely to discontinue statin

therapy within the first three years of use compared with men with the ε2ε3 genotype[32]. Possibly, the efficacy of statins on lipids and lipoproteins is diminished in subjects with the ε4ε4 genotype. Our study confirms that statins have less effect on lipids, but not on angiographic parameters, in subjects carrying the ε4 allele.

The well-reported associations for ApoE genotypes and lipid and lipoprotein levels (i.e. ApoE*4 carriers have higher levels of total and LDL-cholesterol and lower levels of HDL-cholesterol than ApoE*2 carriers) were confirmed in our study cohort. Contrary to most other studies, ApoE4 + carriers did not have higher levels of total and LDL cholesterol compared with ApoE3 carriers. ApoE genotype was not related to the extent of coronary atherosclerosis.

The literature regarding the effect of ApoE genotype on increased susceptibility to cardiovascular risk is conflicting. Most studies have reported a deleterious effect of the ε4 allele on CAD susceptibility[3,5]. These studies, however, were mainly carried out in dyslipidaemic patients. In our normo-lipidaemic or moderately hypercholesterolaemic CAD population we found no evidence of such an association. Subjects with the ε4 allele can either be normolipidaemic or have high LDL-cholesterol levels. In our study the latter group was not present. It is possible that dyslipidaemic ε4 carriers do have increased CAD risk, while normolipidaemic ε4 carriers do not. Other factors such as age, sex, obesity, glucose intolerance or alcohol use can modulate the effect of the different ApoE alleles, suggesting that ApoE exerts its influence mainly when specific environmental conditions are present[25-27].

In conclusion, we have demonstrated that the effects of statins in subjects with different ApoE genotypes were different with regard to the lipoprotein profile, but not with regard to angiographic parameters. Furthermore ApoE did influence lipid and lipoprotein levels, but was not associated with the extent or prevalence of coronary atherosclerosis in normolipidaemic or moderately hypercholesterolaemic men with CAD.

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