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Modulation of Lipoprotein(a) Atherogenicity by High Density Lipoprotein Cholesterol Levels in Middle-Aged Men With Symptomatic Coronary Artery Disease and Normal to Moderately Elevated Serum Cholesterol

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Objectives. **This study sought to examine whether lipoprotein(a) levels predict coronary artery lumen changes in patients with symptomatic coronary artery disease (CAD) and normal to moderate hypercholesterolemia.**

Background. **Recent conflicting reports have confirmed or refuted the association of lipoprotein(a) with clinical events or angiographically verified disease progression.**

Methods. **The association between serum lipoprotein(a) and changes in coronary artery lumen was studied in 704 men entered into the Regression Growth Evaluation Statin Study (REGRESS), a double-blind, placebo-controlled, quantitative angiographic study that assessed the effect of 2 years of pravastatin treatment. The primary end points were changes in average mean segment diameter (MSD) and average minimal obstruction diameter (MOD). Pavastatin- and placebo-treated patients were classified as having progressing, regressing or stable CAD, and median lipoprotein(a) concentrations were compared. Bivariate and multivariate regression analyses were performed in the overall patient group and in high risk subgroups.**

Results. **Pravastatin treatment did not affect serum apolipoprotein(a) levels. Median in-trial (sampled at 24 months) apolipoprotein(a) levels for regressing, stable and progressing CAD were, respectively, 130, 162 and 251 U/liter in placebo-treated patients and 143, 224 and 306 U/liter in pravastatin-treated patients. Predictors of MSD and MOD changes were baseline MSD and MOD, in-trial apolipoprotein(a), in-trial high density lipoprotein (HDL) cholesterol and baseline use of long-acting nitrates. The multivariate models predicted 14% of MSD changes and 12% of MOD changes; apolipoprotein(a) predicted only 2.6% and 4.8%, respectively. However, in patients with in-trial HDL cholesterol levels <0.7 mmol/liter, apolipoprotein(a) predicted up to 37% of the arteriographic changes.**

Conclusions. **Serum lipoprotein(a) levels predict coronary artery lumen changes in normal to moderately hypercholesterolemic white men with CAD; its atherogenicity is marked in the presence of concomitant hypoalphalipoproteinemia.**

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Lipoprotein(a) represents a family of low density lipoprotein (LDL)–like lipoproteins that contain apolipoprotein B_{100} linked by a disulfide bridge to the highly polymorphic glycoprotein apolipoprotein(a). In healthy subjects, serum lipoprotein(a) levels are known to be constant throughout life and are mainly genetically determined (1). Lipoprotein(a) is characterized by an important degree of structural and functional heterogeneity and is postulated to be both atherogenic and thrombogenic—the former because of its high cholesterol content, the latter because of its molecular mimicry of plasminogen (1,2). Its physiologic function is still unknown.

Since the discovery of lipoprotein(a) by Berg in 1963, numerous studies (3–24) have appeared that examined the relation between lipoprotein(a) and coronary artery disease (CAD), including epidemiologic and clinical case-control studies that investigated the association of lipoprotein(a) levels with the presence and severity of CAD, myocardial infarction, restenosis after angioplasty (16) and vein graft occlusion after coronary artery bypass graft surgery (CABG) (17). In most studies (3–17), it was concluded from multivariate analysis that included age, body mass index, blood pressure, cigarette smoking, and high density lipoprotein (HDL) and LDL cholesterol levels that lipoprotein(a) is an independent risk factor for the development of CAD. However, the role of lipoprotein(a) in CAD has also been questioned (18–24). Some of the

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Abbreviations and Acronyms

CABG	=	coronary artery bypass graft surgery
CAD	=	coronary artery disease
HDL	=	high density lipoprotein
LDL	=	low density lipoprotein
MLR	=	multiple linear regression
MOD	=	minimal obstruction diameter
MSD	=	mean segment diameter
PTCA	=	percutaneous transluminal coronary angioplasty
REGRESS	=	Regression Growth Evaluation Statin Study
4S	=	Scandinavian Simvastatin Survival Study

conflicting results may be explained by methodologic confounders (25).

Presently, evidence is accumulating that the challenge of elevated lipoprotein(a) levels may not be as deleterious as previously thought because it appears that whether lipoprotein(a) causes CAD may depend on the interaction of lipoprotein(a) with environmental or genetic factors: 1) Serum lipoprotein(a) levels differ between populations, with median lipoprotein(a) levels approximately twofold to threefold higher in blacks than in whites (26,27). However, in the absence of atherogenic diets, blacks exhibit low morbidity and mortality rates resulting from CAD. Analogous, transgenic mice possessing the apolipoprotein(a) gene developed atherosclerosis only when fed an atherogenic diet but not when fed their normal chow diet (28). 2) In a human angiographic study, Armstrong et al. (3) reported that increased LDL concentrations markedly increased the risk of CAD because of elevated lipoprotein(a) levels, indicating modulation of lipoprotein(a) atherogenicity by LDL cholesterol. 3) Several case-control studies have demonstrated a "positive" association between lipoprotein(a) levels and the presence or severity of CAD only in specific patient subsets, such as those with a parental history of myocardial infarction (6), young men with premature CAD (8,12) and patients with hyperlipidemia (10,11). 4) More conflicting reports have been published lately, confirming or refuting the association of lipoprotein(a) with angiographically verified disease progression or clinical events. Watts et al. (29) and Marburger et al. (30) found that lipoprotein(a) correlated poorly with arteriographic changes over time in patients who underwent a diet and exercise program or received lipid-lowering medication. In contrast, Terres et al. (31) demonstrated that lipoprotein(a) correlated strongly with rapid disease progression in untreated patients. Finally, Thompson et al. (32) showed that lowering both lipoprotein(a) and LDL cholesterol levels in patients with familial hypercholesterolemia produced no greater angiographic benefit than lowering LDL cholesterol levels alone. Consequently, the latter observations appear to detract from the causal importance of lipoprotein(a) relative to LDL in coronary atherosclerosis.

We recently completed a large angiographic lipid intervention trial (Regression Growth Evaluation Statin Study [REGRESS]) (33). The REGRESS database provided us with the opportunity to determine the role of lipoprotein(a) on progression of coronary atherosclerosis in a prospective manner in patients with normal to moderately elevated serum cholesterol levels. We also compared lipoprotein(a) levels of patients in the REGRESS trial with those of healthy control subjects. Furthermore, we aimed to delineate in men with normal to moderately elevated serum cholesterol levels the setting in which lipoprotein(a) most exerts its adverse effects.

Methods

Study design and subjects. REGRESS was a prospective, double-blind, placebo-controlled, multicenter study that assessed the effect of treatment with pravastatin (40 mg/day) on progression and regression of angiographically documented CAD (33). Dutch male patients with symptomatic coronary atherosclerosis who had normal to moderately elevated cholesterol (4 to 8 mmol/liter) and triglyceride (<4 mmol/liter) levels and underwent various forms of primary treatment (percutaneous transluminal coronary angiography [PTCA], CABG, medical treatment) were included. Patients using lipid-lowering drugs ≤6 weeks before qualifying lipid measurement (≤12 weeks for fibric acid derivatives or hepatic hydroxymethyl glutaryl coenzyme A [HMG-CoA] reductase inhibitors) were excluded. All were white. Further details of the enrollment procedure, treatment and follow-up and primary treatment blocks are described elsewhere (33). Lipoprotein(a), quantified by its apolipoprotein(a) content, was determined in a subset of patients who completed the REGRESS main study and from whom leftover serum was available both at baseline and at 24 months. Of the 885 patients originally enrolled in the main trial (33), 95 could not be included in the lipoprotein(a) substudy because of adverse events, premature study discontinuation and death; in another 86, leftover serum was not available either at baseline or at 24 months. The baseline characteristics of the 181 patients not included in the substudy were not significantly different from those of the 704 who were included ($p \geq 0.10$, data not shown). Evaluable baseline and final coronary angiograms were available in 567 patients (81%), a proportion similar to that in the main trial (33). For comparison, apolipoprotein(a) levels were analyzed in 274 unrelated, apparently healthy male control subjects who had no clinical symptoms of CAD. Entry criteria were white race; cholesterol levels between 4 and 8 mmol/liter; 20 kg/m^2 ≤ body mass index ≤30 kg/m^2; no diabetes; no previous history of coronary or cerebral infarction, PTCA, revascularization and cancer; no intake of oral anticoagulant, antihypertensive or lipid-lowering medication; and an intake of less than three glasses of alcoholic beverage per day.

Quantitative coronary arteriography and clinical events. Coronary arteriograms were analyzed by quantitative computer analysis (Cardiovascular Measurement System), as described elsewhere (33). To standardize vasomotor tone, 5 to 10 mg of isosorbide dinitrate was administered sublingually 5 to 10 min before coronary angiography. Primary end points were 1) change in average mean segment diameter (MSD) per

patient, and 2) change in average minimal obstruction diameter (MOD) per patient. If a segment or lesion was adequately visualized in two (preferably orthogonal) projections and free of significant foreshortening in both views, the average values of the variables in both projections were calculated. To calculate the average MSD and MOD per patient, the MSDs and MODs of all qualifying segments or obstructions (up to 13) were added and divided by the number of contributing segments or obstructions. Segments that were occluded or located distal to an occlusion at either baseline or follow-up were not included because no meaningful MSD value could be calculated for these cases. Obstructions that had progressed to occlusion or occlusions that had recanalized were not excluded; segments distal to occlusions were excluded because no meaningful MOD value could be calculated for segments distal to an occlusion. Changes in MSD (n = 562) and MOD (n = 567) were computed using those segments considered not influenced by PTCA or CABG during the trial (33).

Analogous to the main angiographic trial (33), patients were categorized with regard to MOD and clinical events (i.e., nonfatal myocardial infarction and CAD death) as having CAD that regressed, remained stable or progressed, as follows: 1) CAD in patients with at least one lesion worsening by ≥0.4 mm or developing a lesion that reduced the lumen diameter by ≥0.4 mm was categorized as progressing; 2) CAD in patients with at least one lesion improving by ≥0.4 mm and no lesions worsening ≥0.4 mm was classified as regressing; 3) CAD in patients with no lesions worsening or improving by ≥0.4 mm was categorized as stable. Patients with a mixture of regressing and progressing lesions, were considered to have progressing CAD, as well as patients who had a new clinical event, regardless of angiographic outcome.

Specimen collection and storage. The REGRESS main study was ongoing between January 1990 and December 1993. Blood specimens were taken from fasting patients. Serum and plasma were harvested locally after centrifugation. Sera for the core Lipid Reference Laboratory, Rotterdam, The Netherlands, were immediately aliquotted, stored at −20°C and shipped weekly on dry ice. On the week of arrival, sera were thawed for regular serum lipid analyses. Aliquots for serum apolipoprotein(a) analysis were stored frozen at −70°C for a maximum of 2 years.

Fresh-frozen EDTA-plasma was obtained from healthy control subjects. Sampling and randomization was done by the Dutch Institute of Public Health (RIVM, Bilthoven, The Netherlands). Plasma apolipoprotein(a) values were recalculated to serum apolipoprotein(a) values through multiplying by 1.03.

Laboratory measurements. Apolipoprotein(a) was measured with the Pharmacia apolipoprotein(a) radioimmunoassay kit (No. 10-6497-01, Kabi Pharmacia Diagnostics, Uppsala, Sweden). According to the manufacturer, 1 U of apolipoprotein(a) is very approximately equal to 0.7 mg of lipoprotein(a) mass. Serum apolipoprotein(a) determinations were performed at baseline and after 24 months, and paired analyses were available from 704 REGRESS patients (80% of those included in the main study). Throughout the present report, the follow-up apolipoprotein(a) values, as determined from the blood specimens sampled at 24 months, are indicated as in-trial apolipoprotein(a) concentrations. Interassay coefficients of variation varied between 3.5% and 7.3% for low level control samples (130 to 200 U/liter) and between 3.3% and 5.6% for high level control samples (350 to 500 U/liter). Because international standardization is lacking, overlapping lots of frozen serum pools at three different levels (low, medium and high) were analyzed throughout the substudy to ensure "traceability" among different reagent lots. We also verified that freezing sera at −70°C for up to 2 years did not affect measurements of apolipoprotein(a).

Serum cholesterol, HDL cholesterol and triglycerides were measured using standard enzymatic techniques. LDL cholesterol was calculated using the Friedewald formula (34). Because the Friedewald formula does not account for cholesterol associated with lipoprotein(a), estimated LDL cholesterol (mmol/liter) was corrected by subtracting lipoprotein(a)-cholesterol, calculated as [0.30 × Lipoprotein(a) mass/386.65] (35). Serum lipids were analyzed at baseline and after 2, 4, 6, 12, 18 and 24 months of treatment or placebo. In-trial serum lipid concentrations were calculated by averaging serum lipid values obtained per patient during the entire treatment/placebo phase. The Lipid Reference Laboratory maintains cholesterol and HDL cholesterol standardization through the Lipid Standardization Program of the Centers for Disease Control, National Heart, Lung, and Blood Institute, and fulfills its criteria concerning accuracy and precision. The laboratory is also a member of the U.S. Cholesterol Reference Method Laboratory Network (36).

Blood glucose was measured with standard technology in the local hospital laboratories at baseline and at 12 and 24 months. In-trial glucose concentrations were derived by averaging 12- and 24-month glucose values. Baseline plasma fibrinogen was measured centrally with an enzyme immunoassay method (37,38).

Statistical analysis. The Student *t* test, Mann-Whitney test or Pearson chi-square test was used to compare group mean values or medians, or both. Analysis of variance or Kruskall-Wallis tests were used to compare different patient groups. The natural logarithms of triglycerides, fibrinogen and apolipoprotein(a) and the LDL cholesterol/HDL cholesterol ratio were used to normalize distributions; baseline MOD and MOD changes were ranked because of their skewness.

Bivariate relations were quantified with Pearson or Spearman rank correlation coefficients. Multiple linear regression (MLR) analyses were used to estimate the effects of individual variables independent of others; partial correlations were used to quantify the relation between two variables, independent of others. Squared partial correlation coefficients, multiplied by 100, were calculated to estimate the percentage of arteriographic changes explained by individual variables. Stepwise forward selection was used to build up the MLR model. The criterion for a variable to enter and remain in the model was an initial probability value in the presence of other variables not

exceeding 0.05. F statistics were used for the selection process. As a last step, interactions between the remaining variables in the final model were tested. Throughout the study the adopted significance level was p = 0.05.

Results

Baseline characteristics. Baseline characteristics of the 704 REGRESS patients studied are presented in Table 1 (mean [±SD] age 56 ± 8 years, range 31 to 70; body mass index 26.0 ± 2.7 kg/m^2; systolic blood pressure 135 ± 18 mm Hg, diastolic blood pressure 82 ± 10 mm Hg). Approximately 89% of participants had previously smoked, and 28% were current smokers. Fifty-one percent of patients were randomized to pravastatin treatment. Baseline coronary scores could be computed for 702 patients; two baseline angiograms were lost. The average MSD was 2.55 mm, and the average MOD was 1.89 mm. The overall baseline median (25th, 75th percentiles) apolipoprotein(a) concentration was 236 (91, 665) U/liter. Serum apolipoprotein(a) concentrations were ≥286 U/liter in 45% and ≥430 U/liter in 38% of patients, which was approximately equal to 200 and 300 mg/liter of lipoprotein(a) mass, the generally accepted cutoff values for elevated CAD risk. Baseline median apolipoprotein(a) levels did not significantly differ between patients randomized to pravastatin or placebo treatment (p = 0.84). Mean baseline cholesterol and HDL cholesterol levels were, respectively, 6.04 and 0.93 mmol/liter.

In the male control group (n = 274), mean age was 50 ± 7 years, body mass index 25.0 ± 2.4 kg/m^2, systolic blood pressure 122 ± 13 mm Hg and diastolic blood pressure 77 ± 9 mm Hg (data not shown). Approximately 77% of the participants had previously smoked, and 45% were current smokers. Mean alcohol intake was 1.14 beverages/day. Median (25th, 75th percentiles) apolipoprotein(a) was 136 (65, 485) U/liter. Mean cholesterol and HDL cholesterol levels were 5.66 and 1.11 mmol/liter, respectively. After adjusting for age, body mass index, systolic and diastolic blood pressure, alcohol intake and smoking habits, apolipoprotein(a) mean values were 300 U/liter in the control group versus 418 U/liter in the REGRESS patient group (p = 0.0004). Adjusted mean cholesterol and HDL cholesterol values were, respectively, 5.71 and 1.13 mmol/liter in the control group and 6.07 and 0.92 mmol/liter in the patient group; p values for the differences between adjusted mean values were 0.0044 and <0.0001 for serum cholesterol and HDL cholesterol, respectively.

In-trial serum apolipoprotein(a) levels in placebo- and pravastatin-treated patients. Median baseline apolipoprotein(a) levels were 238 and 236 U/liter in the placebo and pravastatin groups, respectively (Table 1); at study end, median apolipoprotein(a) levels in placebo- and pravastatin-treated patients were 217 and 219 U/liter, respectively (p = NS, data not shown). Spearman rank correlation between baseline and follow-up apolipoprotein(a) levels was 0.96. Although pravastatin did not significantly influence median apolipoprotein(a) levels, it significantly reduced mean cholesterol, LDL cholesterol and triglyceride levels and increased mean HDL cholesterol levels compared with placebo (p < 0.001); the maximal pravastatin effect was reached 3 to 4 weeks after starting therapy (33).

Table 1. Baseline Characteristics of the 704 Patients From the REGRESS Main Study

	Overall (n = 704)	Placebo Group (n = 346)	Pravastatin Group (n = 358)	p Value*
Clinical data				
Age (yr)	56 ± 8	55 ± 8	57 ± 8	0.03
SBP (mm Hg)	135 ± 18	135 ± 19	135 ± 17	0.98
DBP (mm Hg)	82 ± 10	82 ± 10	81 ± 9	0.14
BP ≥160/95 mm Hg	123 (18%)	64 (19%)	59 (17%)	0.48
HTN by history	193 (27%)	103 (30%)	90 (25%)	0.17
Current smoker	194 (28%)	94 (27%)	100 (28%)	0.82
Ex-smoker	624 (89%)	301 (87%)	323 (90%)	0.18
BMI (kg/m^2)	26.0 ± 2.7	26.2 ± 2.7	25.8 ± 2.8	0.10
≥30 kg/m^2	60 (9%)	33 (10%)	27 (8%)	0.32
Long-acting nitrates	391 (56%)	191 (55%)	200 (56%)	0.86
Beta-blockers	509 (72%)	253 (73%)	256 (72%)	0.63
Ca channel blockers	425 (60%)	207 (60%)	218 (61%)	0.77
Familial heart disease	345 (49%)	168 (49%)	177 (49%)	0.81
History of MI	327 (46%)	154 (45%)	173 (48%)	0.31
History of PTCA	44 (6.3%)	22 (6.0%)	22 (6.0%)	0.91
Angiographic data				0.51
1 VD	300 (43%)	154 (45%)	146 (41%)	
2 VD	234 (33%)	114 (33%)	120 (34%)	
3 VD	168 (24%)	77 (22%)	91 (26%)	
MSD (mm)	2.55 ± 0.40	2.56 ± 0.41	2.54 ± 0.38	0.47
MOD (mm)	1.89 ± 0.34	1.91 ± 0.34	1.88 ± 0.34	0.27
Laboratory data				
Apo(a) (U/liter)	415 ± 422	430 ± 442	400 ± 402	0.86
Median	236	238	236	
Total-C (mmol/liter)	6.04 ± 0.87	6.06 ± 0.86	6.02 ± 0.88	0.56
HDL-C (mmol/liter)	0.93 ± 0.23	0.92 ± 0.22	0.94 ± 0.23	0.28
LDL-C (mmol/liter)	4.31 ± 0.79	4.32 ± 0.79	4.30 ± 0.79	0.61
Corrected LDL-C (mmol/liter)†	4.09 ± 0.79	4.11 ± 0.77	4.07 ± 0.80	0.57
TGs (mmol/liter)	1.94 ± 0.71	1.97 ± 0.72	1.92 ± 0.69	0.47
LDL-C/HDL-C ratio	4.88 ± 1.40	4.94 ± 1.43	4.83 ± 1.38	0.54
Blood glucose (mmol/liter)	5.36 ± 1.31	5.27 ± 1.15	5.44 ± 1.45	0.08
Fibrinogen (g/liter)	3.36 ± 1.42	3.45 ± 1.43	3.28 ± 1.42	0.21

*Student *t* test, Pearson chi-square test or Mann-Whitney test, as appropriate, for pravastatin versus placebo treatment. †Corrected for lipoprotein(a)-cholesterol and calculated as Total-C (mmol/liter) − HDL-C (mmol/liter) − [TGs (mmol/liter/2.2] − {[Apo(a) (U/liter) * 0.7 * 0.3]/386.65}. Data presented are mean value ± SD or number (%) of patients, unless otherwise indicated. Apo(a) = apolipoprotein(a); BMI = body mass index; BP = blood pressure; Ca = calcium; DBP = diastolic blood pressure; HDL-C = high density lipoprotein cholesterol; HTN = hypertension; LDL-C = low density lipoprotein cholesterol; MOD = minimal obstruction diameter; MSD = mean segment diameter; PTCA = percutaneous transluminal coronary angioplasty; REGRESS = Regression Growth Evaluation Statin Study; SBP = systolic blood pressure; TGs = triglycerides; Total-C = total cholesterol; VD = vessel disease.

In-trial serum apolipoprotein(a) and metabolic variables in patients showing progression, no change or regression during the 2-year follow-up period. Table 2 demonstrates median in-trial serum apolipoprotein(a) levels in patients with regressing, stable and progressing CAD. In placebo-treated

Table 2. Serum Apolipoprotein(a) and Other Laboratory Findings in 567 Patients With Regressing, Stable or Progressing Coronary Artery Disease*

	Pravastatin Group			
	Regressing CAD (n = 45)	Stable CAD (n = 108)	Progressing CAD (n = 128)	p Value†
Apo(a) (U/liter)	143 (8–1,573)	224 (10–2,295)	306 (5–1,627)	0.34
Total-C (mmol/liter)	4.46 (3.23–7.06)	4.88 (2.78–7.31)	4.87 (3.11–9.91)	0.04
LDL-C (mmol/liter)	2.98 1.83–4.46)	3.13 (1.56–5.52)	3.28 (1.56–5.97)	0.03
Corrected LDL-C (mmol/liter)	2.69 (1.70–4.39)	2.87 (1.33–5.51)	3.12 (1.21–5.72)	0.09
HDL-C (mmol/liter)	0.99 (0.55–1.59)	0.95 (0.55–1.91)	1.03 (0.55–1.91)	0.54
LDL-C/HDL-C ratio	2.99 (1.55–6.64)	3.15 (1.09–8.49)	3.32 (1.37–10.85)	0.06
TGs (mmol/liter)	1.34 (0.48–4.32)	1.31 (0.44–5.65)	1.30 (0.45–7.10)	0.70
Blood glucose (mmol/liter)	5.3 (4.2–11.1)	5.0 (3.4–12.6)	5.20 (3.30–11.0)	0.36
Baseline fibrinogen (g/liter)	3.12 (2.04–5.91)	3.02 (1.30–8.40)	2.98 (1.16–8.42)	0.10
	Placebo Group			
	Regressing CAD (n = 27)	Stable CAD (n = 95)	Progressing CAD (n = 164)	p Value†
Apo(a) (U/liter)	130 (6–1,236)	162 (5–1,677)	251 (5–2,143)	0.0067
Total-C (mmol/liter)	6.30 (3.43–8.52)	6.14 (3.77–8.43)	6.06 (2.99–8.79)	0.58
LDL-C (mmol/liter)	4.34 (1.84–6.86)	4.39 (2.46–6.51)	4.37 (1.78–6.74)	0.68
Corrected LDL-C (mmol/liter)‡	4.17 (1.82–6.76)	4.22 (2.20–6.41)	4.11 (1.69–6.67)	0.42
HDL-C (mmol/liter)	0.94 (0.58–1.82)	0.88 (0.56–1.58)	0.86 (0.42–2.14)	0.61
LDL-C/HDL-C ratio	4.62 (1.59–8.30)	4.93 (2.59–8.86)	5.05 (1.67–11.64)	0.55
TGs (mmol/liter)	1.74 (0.45–5.90)	1.57 (0.57–7.10)	1.37 (0.38–7.60)	0.10
Blood glucose (mmol/liter)	5.1 (4.1–7.1)	5.10 (3.6–10.2)	5.2 (3.4–9.0)	0.97
Baseline fibrinogen (g/liter)	2.68 (1.28–6.61)	3.19 (1.03–7.79)	3.29 (1.27–7.73)	0.038

*See methods for definition of progressing, stable and regressing coronary artery disease (CAD). †Kruskal-Wallis test. ‡Corrected for lipoprotein(a)-cholesterol and calculated as in Table 1. Data presented are median (range) in-trial concentrations, unless otherwise indicated. Other abbreviations as in Table 1.

patients, apolipoprotein(a) levels differed significantly among categories; median apolipoprotein(a) levels were 1.2-fold higher for stable CAD and 1.9-fold higher for progressing CAD compared with regressing CAD ($p = 0.0067$). Although a similar trend was found among categories in the pravastatin-treated group (i.e., median apolipoprotein(a) levels were 1.6-fold higher for stable CAD and 2.1-fold higher for progressing CAD), the differences were not significant ($p = 0.34$). Overall median apolipoprotein(a) levels were 143, 177 and 259 U/liter, respectively, in patients with regressing, stable and progressing CAD ($p = 0.0075$, data not shown).

In placebo-treated patients, median in-trial serum lipid levels did not differ among categories, whereas fibrinogen did ($p = 0.038$). In pravastatin-treated patients, total and LDL cholesterol differed among groups. However, after correction for lipoprotein(a)-cholesterol, differences in median LDL cholesterol levels became insignificant.

Correlates and predictors of coronary score changes. Bivariate correlation analysis demonstrated that baseline MOD, baseline MSD, baseline use of long-acting nitrates and allocation to pravastatin were significant correlates to coronary score changes. Baseline and in-trial apolipoprotein(a) levels correlated significantly with MOD changes but not with MSD changes. In-trial serum lipid levels were more consistently and more closely related to arteriographic changes than were baseline serum lipid levels (data not shown).

After adjustment for the variables shown in Table 3, apolipoprotein(a) became significantly correlated with both MOD and MSD changes. Other predictors were in-trial HDL cholesterol, baseline MSD, baseline MOD and baseline use of long-acting nitrates. Overall, the MLR models predicted 14% of MSD changes and 12% of MOD changes; by itself, in-trial apolipoprotein(a) predicted 2.6% of MSD changes and 4.8% of MOD changes ($p < 0.01$). From table 3 it becomes obvious that because of entering in-trial serum lipid concentrations into the model, allocation to pravastatin no longer predicted MOD or MSD changes.

In Table 4 the magnitude of the effect of in-trial apolipoprotein(a) on arteriographic changes is demonstrated after adjusting for significant covariates only. From the beta-coefficients of the MLR equation it can be estimated that the mean MSD decrease per patient is 0.022 mm/ln[apolipoprotein(a)] increment and 0.060 mm/0.5-mmol/liter HDL cholesterol decrease. Analogously, mean MOD decrease per patient is estimated to be 0.025 mm/ln[apolipoprotein(a)] increment and 0.038 mm/0.5-mmol/liter HDL cholesterol decrease (derived from unranked MOD data, not shown).

Table 3. Relations Between Adjusted Coronary Score Changes and Clinical and Laboratory Findings: Results of Multiple Regression Analyses

	ΔMSD (n = 562)	ΔMOD (n = 567)
Baseline MSD	0.28*	
Baseline MOD		0.27*
Age	0.00	0.13†
BMI	− 0.02	− 0.01
Current smoker	0.08	0.05
Ex-smoking	0.08	0.08
SBP	− 0.08	− 0.09
DBP	0.08	0.10
Long-acting nitrates	0.22*	0.12
Pravastatin	− 0.03	− 0.07
In-trial Apo(a)	0.16‡	0.22*
In-trial corrected LDL-C§	0.05	0.02
In-trial HDL-C	− 0.17‡	− 0.14†
In-trial TGs	− 0.08	− 0.01
In-trial blood glucose	0.08	0.09
Baseline fibrinogen	− 0.03	0.00
Multiple R	0.43	0.41
Adjusted R^2	14%	12%

*$p < 0.001$. †$p < 0.05$. ‡$p < 0.01$. §Corrected for lipoprotein(a)-cholesterol and calculated as in Table 1. Data presented are partial correlation coefficients, adjusted for all other variables in table, for changes (Δ) in mean segment diameter (MSD) and ranked minimal obstruction diameter (MOD). Other abbreviations as in Table 1.

Modulation of apolipoprotein(a) atherogenicity by the lipoprotein milieu? Apolipoprotein(a) atherogenicity was investigated in high risk subgroups (Table 5). Stratifications were made using the 10th percentile value of in-trial HDL cholesterol and the 90th percentile values of in-trial LDL cholesterol (corrected), triglycerides and LDL cholesterol/HDL cholesterol ratios (n = 704). Table 5 demonstrates that in-trial serum apolipoprotein(a) correlates much stronger with adjusted MSD and MOD changes in patients with in-trial HDL cholesterol <0.7 mmol/liter, explaining 30% and 37%, respectively, of their variance ($p < 0.01$). In contrast, in the subgroup with in-trial LDL cholesterol ≥4.96 mmol/liter, only 1% and 2% of the MSD and MOD changes could be explained by serum apolipoprotein(a) (p = NS).

Modulation of apolipoprotein(a) atherogenicity by in-trial HDL cholesterol levels is presented in Figure 1. Scattergrams display adjusted MOD and MSD reductions versus ln[apolipoprotein(a)] for the two HDL cholesterol strata. The steep slope of the regression line in the low HDL subgroup (<0.7 mmol/liter) compared with the moderate slope in the higher HDL subgroup (≥0.7 mmol/liter) reflects enhanced progression of CAD at similar apolipoprotein(a) levels in the low HDL subgroup. In the low HDL subgroup, the intersection of the regression lines with the line of no progression or regression coincides, for both MOD and MSD changes, with an ln[apolipoprotein(a)] of ~2 [i.e., as low as 7 U/liter apolipoprotein(a)]. In the lower risk stratum, similar albeit weaker trends were found across the measured serum apolipoprotein(a) range; however, no clear cutoff apolipoprotein(a) value above which most CAD progressed could be demonstrated.

Discussion

The consistent clinical lesson from current arteriographic trials is that patients with documented CAD benefit from aggressive lipoprotein manipulations with regard to both coronary artery lumen change and clinical events (39), irrespective of the baseline cholesterol level. Subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) (40) showed that percent reductions in LDL cholesterol and decreases in relative risk of coronary heart disease in patients taking simvastatin were comparable and constant across all quartiles of baseline LDL cholesterol, suggesting that the percent reduction in LDL cholesterol rather than its absolute level during treatment was the determinant of clinical benefit. Thompson et al. (41) further tested this hypothesis across 11 quantitative angiographic trials and found a significant relation between percent change in LDL cholesterol and change in percent diameter stenosis. However, this precept was tempered by the results of the Harvard Atherosclerosis Reversibility Project (HARP) (42), in which lipid-lowering appeared ineffectual in patients whose baseline values of LDL cholesterol were in the normal range. Taken together, the 4S data and analyses of quantitative coronary angiographic trials suggest (41) that although lowering LDL cholesterol by 35% often helps to slow or halt progression of atherosclerosis, it does not always do so. This finding presumably reflects the importance of other risk factors for which lipoprotein(a) is a candidate in promoting lesion progression. Because only few prospective angiographic

Table 4. Predictors of Arteriographic Changes (minimal obstruction diameter, mean segment diameter) in the 567 Patients From the REGRESS Main Study: Results of Stepwise Forward Multiple Linear Regression Analysis*

Dependent Variable	Regression Coeff (SE)	p Value	Adjusted R^2 (%)
ΔMSD			
Baseline MSD	0.112 (0.024)	< 0.0001	6.5
Long-acting nitrates	0.080 (0.022)	0.0003	10.1
In-trial HDL-C	− 0.120 (0.043)	0.0057	12.0
In-trial Apo(a) (ln)	0.022 (0.008)	0.0070	13.9
Constant	0.278 (0.095)	0.0036	
ΔMOD (ranked)			
Baseline MOD	0.247 (0.055)	< 0.0001	5.6
In trial Apo(a) (ln)	22.47 (6.41)	0.0005	8.9
In-trial HDL-C	− 82.48 (33.11)	0.0133	10.4
Long-acting nitrates	37.81 (17.56)	0.0321	11.5
Constant	153.0 (50.47)	0.0027	

*Baseline minimal obstruction diameter (MOD); baseline mean segment diameter (MSD); age; body mass index; current and previous smoking; systolic and diastolic blood pressures; use of long-acting nitrates; allocation to pravastatin; baseline fibrinogen levels; and in-trial serum levels of apolipoprotein(a) [Apo(a)], low density lipoprotein cholesterol, high density lipoprotein cholesterol (HDL-C), triglycerides and blood glucose were the variables entered into the model. Coeff = coefficient; Δ = change in.

Table 5. Correlations Between In-Trial Serum Apolipoprotein(a) Levels and Changes in Coronary Scores in Selected Strata: Results of Bivariate and Multivariate Correlation Analyses

	ΔMSD (n = 562)				ΔMOD (n = 567)			
Stratification*	No. of Pts	Pearson Corr Coeff	No. of Pts	Partial Corr Coeff†	No. of Pts	Pearson Corr Coeff	No. of Pts	Partial Corr Coeff†
HDL-C <0.70 mmol/liter	51	0.27‡	28	0.55§	52	0.31§	30	0.61‖
HDL-C ≥0.70 mmol/liter	501	0.04	238	0.11	505	0.10‡	242	0.18§
TGs ≥2.74 mmol/liter	53	0.24	20	0.44	57	0.37§	22	0.27
TGs <2.74 mmol/liter	499	0.04	248	0.14‡	500	0.08	250	0.20§
LDL-C ≥4.96 mmol/liter¶	60	− 0.06	32	0.01	61	− 0.01	33	0.14
LDL-C <4.96 mmol/liter¶	482	0.09	236	0.17‡	486	0.13§	239	0.23‖
LDL-C/HDL-C ratio ≥6.11¶	55	0.28‡	33	0.40	56	0.12	34	0.34
LDL-C/HDL-C ratio <6.11¶	487	0.04	237	0.15‡	491	0.11‡	240	0.21§

*Cutoff values for risk stratification were based on the 10th percentile in-trial value for high density lipoprotein cholesterol (HDL-C) and the 90th percentile in-trial values for low density lipoprotein cholesterol (LDL-C), triglycerides (TGs) and LDL-C/HDL-C ratio. †Model variables controlled for: baseline mean segment diameter (MSD); baseline minimal obstruction diameter (MOD); age, body mass index; smoking habits; systolic and diastolic blood pressure; pravastatin treatment; use of long-acting nitrates; baseline fibrinogen and in-trial blood glucose; but serum LDL-C, HDL-C and TG levels. ‡$p < 0.05$. §$p < 0.01$. ‖$p < 0.001$. ¶Corrected for lipoprotein(a)-cholesterol and calculated as in Table 1. Corr Coeff = correlation coefficient; Pts = patients; Δ = change in.

studies have hitherto examined the association of serum lipoprotein(a) with the course of CAD (29–32,43), we aimed to define, in a broader range of patients with documented CAD, in which patients with lipoprotein(a) assessments had the highest predictive value. To this end, apolipoprotein(a) levels were determined in adequately stored leftover sera from REGRESS patients (33).

Pooled data analysis. There are three main results of this substudy: 1) Median baseline apolipoprotein(a) levels were significantly elevated in the REGRESS patient group, who all had symptomatic CAD, compared with levels in healthy control subjects (236 vs. 136 U/liter, $p < 0.001$); furthermore, median in-trial apolipoprotein(a) levels were significantly higher in patients with progressing (259 U/liter) and stable CAD (177 U/liter) than in patients with regressing CAD (143 U/liter). 2) In-trial apolipoprotein(a) and in-trial HDL cholesterol, but not in-trial LDL cholesterol, predicted the course of CAD in normal to moderately hypercholesterolemic men. 3) Apolipoprotein(a) atherogenicity was far more daunting in the presence of concomitant low HDL cholesterol levels (<10th percentile).

The rightward shift of the serum apolipoprotein(a) distribution in the REGRESS patient group compared with that in apparently healthy control subjects is in accordance with the findings of numerous population and clinical studies (3–17). The significantly higher apolipoprotein(a) levels in patients categorized as having progressing or stable CAD than those with regressing CAD (Table 2) are in agreement with the data of Terres et al. (31) but in contrast with the data of Watts et al. (29) and Marburger et al. (30). When in-trial serum lipid levels rather than baseline lipid levels were entered into the MLR models, both in-trial apolipoprotein(a) and in-trial HDL cholesterol, but not in-trial LDL cholesterol, predicted arteriographic changes (Tables 3 and 4) in this patient group. This finding is not surprising in view of the constellation of serum lipids present in the REGRESS population. In fact, decreased HDL cholesterol levels (<0.90 mmol/liter), preexisting in ~50% of the REGRESS population (Table 1), and elevated apolipoprotein(a) levels were major characteristics of its risk profile in addition to moderate baseline hypercholesterolemia. Moreover, the cholesterol-lowering intervention with pravastatin in 50% of patients, mainly affecting LDL cholesterol levels, further diminished the causal role of LDL as a risk factor.

Subgroup analysis. Although apolipoprotein(a) was a predictor of MSD and MOD changes in the studied REGRESS patients, it explained only 2.6% and 4.8% of coronary score changes (Table 3). In the case of concomitant presence of in-trial HDL cholesterol <0.7 mmol/liter, the strength of the association increased greatly, predicting up to 30% and 37% of adjusted MSD and MOD changes (Fig. 1, Table 5).

By delineating other adverse lipoprotein milieus, our results extend the findings of Armstrong et al. (3) and Maher et al. (44) in selected hypercholesterolemic patients in whom the dependence of apolipoprotein(a) atherogenicity on serum LDL cholesterol levels was described. Although modulation of apolipoprotein(a) atherogenicity by in-trial LDL cholesterol levels was present in the REGRESS patient group, it was less prominent than the modulation by in-trial HDL cholesterol (Table 5). Moreover, our data suggest that differences in lipoprotein milieus and other covariates may explain discrepancies between studies investigating the association between lipoprotein(a) levels and CAD course (29–32). Also, whereas Maher et al. (44) documented that arterial benefits of a substantial (>10%) reduction in LDL cholesterol was significant only in patients with lipoprotein(a) levels in at least the 90th percentile, we found, even at low apolipoprotein(a) levels, a deleterious effect of the lipoprotein(a) level on coronary lumen changes in the low HDL subgroup.

In-trial serum lipid concentrations. Because in-trial serum lipid levels correlated more closely with changes in MOD and MSD than baseline serum lipid levels (data not shown), in-trial serum lipid concentrations were used throughout this report to examine the association between apolipoprotein(a) levels and CAD course. Also, patient data were pooled to form a single

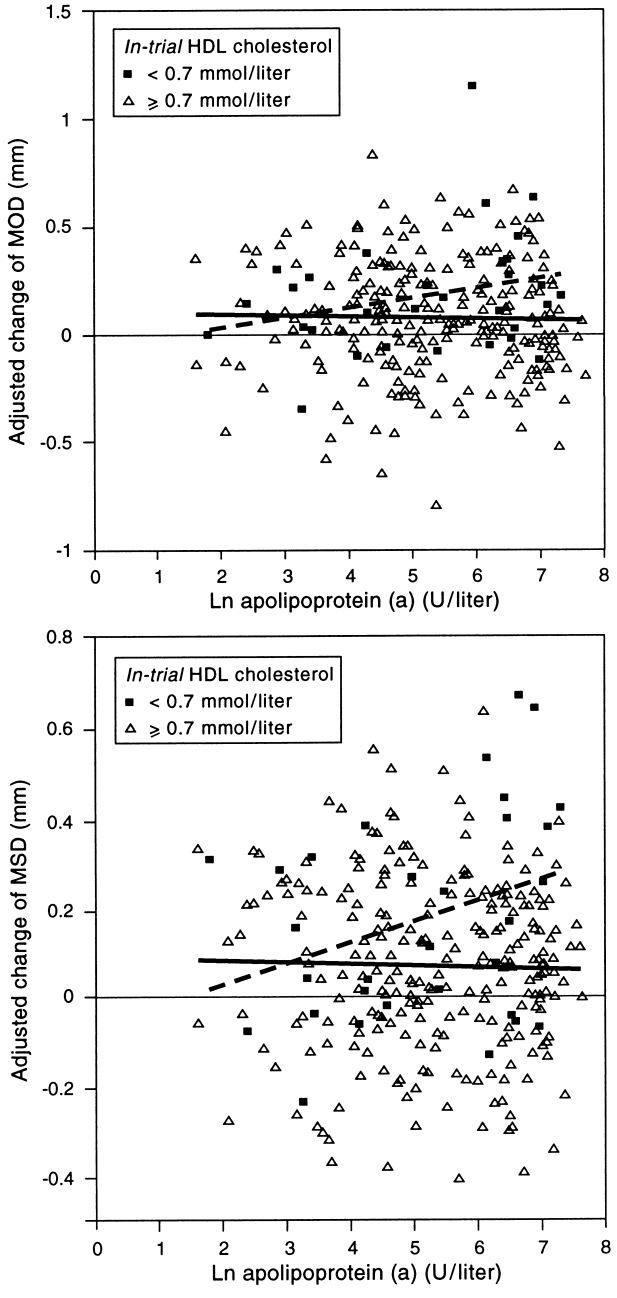

Figure 1. Partial correlation between in-trial serum apolipoprotein(a) levels and changes in MOD (**top**) and MSD (**bottom**) in selected HDL cholesterol strata (HDL cholesterol cutoff: 0.7 mmol/liter). The model variables controlled for are baseline MSD, baseline MOD, age, body mass index, smoking status, systolic and diastolic blood pressures, pravastatin treatment, use of long-acting nitrates, baseline fibrinogen, in-trial blood glucose and in-trial serum LDL cholesterol, HDL cholesterol and triglyceride levels. In the low HDL cholesterol subgroup, the partial correlation coefficients for changes in MOD (**top**) and MSD (**bottom**) versus ln[apolipoprotein(a)] are 0.61 ($p = 0.0004$) and 0.55 ($p = 0.003$), respectively.

collective database because serum apolipoprotein(a) levels were not affected by pravastatin treatment (median levels after 2 years of follow-up: 217 U/liter in control subjects vs. 219 U/liter in patients) and because allocation to pravastatin therapy no longer predicted arteriographic changes in multivariate models in which in-trial serum lipid levels were entered as covariates (Tables 3 and 4). However, so as not to overlook any direct effect of pravastatin treatment on CAD course (45), adjustments for allocation to pravastatin were made. The finding that baseline use of long-acting nitrates seemed to be independently associated with the course of CAD probably reflected a less favorable clinical outcome in patients with more severe disease.

Study advances and limitations. To our knowledge, this is the first prospective angiographic study of this size in a wide range of patients with manifest CAD and normal to moderately elevated cholesterol levels to delineate the lipoprotein milieus that restrain or reinforce apolipoprotein(a) atherogenicity. Another advantage is related to the fact that LDL cholesterol was corrected for lipoprotein(a)-cholesterol, allowing us to distinguish the differential effects of these lipoproteins on the course of CAD. Furthermore, because all apolipoprotein(a) measurements were performed within 2 years, apolipoprotein(a) results were not confounded by lipoprotein(a) degradation due to long-term storage (25). Limitations of this substudy are related to the fact that we do not yet know whether the atherothrombogenicity of lipoprotein(a) is adequately measured by total lipoprotein(a) or apolipoprotein(a) concentrations alone. Future studies should investigate the genetically determined structural or functional polymorphism of lipoprotein(a), or both. Also, the number of major clinical events was too small (n = 12) to examine the association of apolipoprotein(a) levels with patient outcome (4 [1.1%] of 358 in the pravastatin-treated group, 8 [2.3%] of 346 in the placebo-treated group, data not shown). However, because angiographic changes strongly correlate with future coronary events (46–48), it is also realistic to anticipate in this population an effect of apolipoprotein(a) levels on clinical events with longer follow-up.

Conclusions. Lipoprotein(a) is a predictor of coronary artery lumen changes in normal to moderately hypercholesterolemic white men; its atherogenicity is very pronounced in the presence of concomitant hypoalphalipoproteinemia.

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