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Effects of Combination Lipid Therapy on Coronary Stenosis Progression and Clinical Cardiovascular Events in Coronary Disease Patients with Metabolic Syndrome: A Combined Analysis of the Familial Atherosclerosis Treatment Study (FATS), the HDL-Atherosclerosis Treatment Study (HATS), and the Armed Forces Regression Study (AFREGS)

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Abstract

We examined the impact of metabolic syndrome (MS) on coronary stenosis progression and major cardiovascular (CV) events and investigated the mitigating effects of low-density lipoprotein cholesterol (LDL-C) lowering and LDL-C-lowering plus high-density lipoprotein cholesterol (HDL-C) raising. This analysis combined individual patient data from 445 subjects who participated in 3 double-blinded, randomized, placebo-controlled trials (FATS, HATS, and AFREGS) comparing intensive lipid therapy to placebos on coronary stenosis progression by quantitative coronary angiography and on major CV events. The primary endpoints were the change in mean proximal coronary diameter stenosis ($\Delta\%S_{\text{prox}}$) over 3 years and the frequency of the pre-defined composite of coronary artery disease (CAD) death, nonfatal myocardial infarction (MI), stroke and revascularization due to worsening ischemia. Patients with the MS had 50% more rapid coronary stenosis progression and 64% increased CV event frequency compared to those without. More rapid coronary stenosis progression was significantly and independently associated with 3.5-fold increased event risk ($p<0.001$). Combination lipid therapy significantly decreased stenosis progression by 83% ($\Delta\%S_{\text{prox}}=0.5$ vs. 2.9, $p<0.001$) in patients with MS, and induced a small net regression in those without ($\Delta\%S_{\text{prox}}=-0.3$ vs. 2.0, $p<0.001$). Combination therapy reduced the event rate by 54% (13 vs. 28%, $p=0.03$) in those with MS and by 82% (3 vs. 17%, $p=0.002$) without. On average, each 10% reduction in LDL-C or 10% increase in HDL-C was significantly associated with 0.3 $\Delta\%S_{\text{prox}}$ reduction. Each 10% LDL-C-lowering or 10% HDL-C-raising was associated with 11% ($p=0.02$) or

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22% ($p<0.001$) event risk reduction. In conclusion, patients with MS have significantly more rapid coronary stenosis progression and a higher frequency of CV events. Greater stenosis progression rate is associated with a higher event rate. LDL-C-lowering and HDL-C-raising therapies independently and significantly decrease coronary stenosis progression and reduce CV events.

Keywords

metabolic syndrome; coronary artery disease; cardiovascular events; lipid therapy

INTRODUCTION

Clinically popular LDL-focused therapies reduce LDL particle numbers and LDL-C, while HDL-C-raising regimens favorably alter HDL-C, triglycerides and LDL particle size/buoyancy. Thus, drug combinations which do both promise to provide greater benefits than individual therapies alone. To examine this hypothesis, we have combined individual patient data from 3 randomized, double-blind, placebo-controlled angiographic trials with similar design and endpoints, the Familial Atherosclerosis Treatment Study (FATS) (1), the HDL-Atherosclerosis Treatment Study (HATS) (2), and the Armed Forces Regression Study (AFREGS) (3), each of which compared intensive combinations of HDL-C-raising and LDL-C-lowering versus placebos over 3 years in terms of coronary stenosis progression and major CV events in patients with and without the MS.

METHODS

A total of 445 subjects with clinically established or anatomically demonstrated CAD who participated in FATS (which completed in 1989), in AFREGS (in 1996) and in HATS (in 1999) were included in this analysis.

FATS enrolled 146 men, ≤ 62 years of age between January 1984 and February 1987, with elevated apoB levels (≥ 125 mg/dl) and a family history of CAD. All subjects had evidence of coronary atherosclerosis on their baseline angiograms with at least one $\geq 50\%$ stenosis or 3 lesions of $\geq 30\%$ diameter stenosis.

HATS enrolled 160 men (age < 63 years) and women (< 70) with clinical CAD (defined as previous MI, percutaneous coronary intervention or coronary bypass surgery, or confirmed angina), with angiographically confirmed coronary obstruction (at least one $\geq 50\%$ stenosis or 3 lesions at $\geq 30\%$ stenosis), and with low levels of HDL-C (≤ 35 mg/dl in men and ≤ 40 mg/dl in women) between January 1995 and January 1997.

AFREGS recruited 143 military retirees < 76 years of age with angiographically measurable stenosis between 30% and 80% and HDL-C levels < 40 mg/dl in 1993.

Table 1 summarizes the patient characteristics, designated therapies, achieved lipid response and results in angiographic and clinical endpoints for these 3 trials. Despite the differences in many patient characteristics and achieved lipid response among these 3 studies, all showed angiographic and clinical benefits of the lipid therapy.

National Cholesterol Education Program ATP III (4) currently defines the MS as having any 3 or more of the following 5 criteria: (1) abdominal obesity: waist circumference ≥ 102 cm (40 inches) in men and ≥ 88 cm (35 inches) in women; (2) triglycerides ≥ 150 mg/dl; (3) HDL-C < 40 in men or < 50 in women; (4) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or treated hypertension; and (5) high fasting glucose ≥ 100 mg/dl or on drug treatment for elevated glucose. However, waist circumference was not measured in any

of these early studies. For this analysis waist circumference was derived from the body mass index (BMI) value using a linear regression equation of BMI and waist circumference in 2283 VA-HIT subjects (5): waist (cm) = $2.096 \times \text{BMI (kg/M}^2\text{)} + 40.355$ ($r = 0.995$).

Coronary angiography was performed following sublingual nitroglycerin at baseline and was repeated at the final angiogram using a defined sequence of viewing angles. As described previously (1) a detailed coronary map was drawn that included all lesions causing stenosis of at least 15% of the luminal diameter. The lesion causing the most severe stenosis (including **no** stenosis) in each of 9 standard proximal segments was measured using computer-assisted methods in each patient at both baseline and a follow-up coronary angiography at 2.5–3 years. All measurements were done blinded to patient identity, therapy, and the temporal sequence of the paired angiograms. The mean stenosis was averaged among the 9 proximal lesions to give $\Delta\%S_{\text{prox}}$ for each patient. The mean absolute change in the severity of these 9 proximal stenoses, between the 2 angiograms ($\Delta\%S_{\text{prox}}$) was the pre-specified primary endpoint of these studies. (1–3) All such analyses were completed in the University Of Washington Quantitative Angiography Laboratory using identical methods.

The pre-specified primary clinical endpoint was the time to the first of the following events: death from CAD, nonfatal MI, stroke or revascularization for worsening ischemia. These events were collected at each clinical visit. Each event was documented by medical records and was adjudicated by a panel without knowledge of patient randomized therapy, lipid response or coronary angiographic information.

Means and standard deviations (SD) of important patient characteristics were calculated for each of the 3 studies and for patients with and without the MS in the combined dataset. Because the 3 studies (FATS, HATS and AFREGS) differed somewhat in the averaged patient characteristics, length and outcomes, all models and comparisons in this analysis were adjusted for the study effect. (6,7) This was done to prevent confounding of the relationship between the risk factors and outcomes, due merely to differences among the 3 studies. The adjustment was implemented by introducing terms for the 3 category indicator variables for the study (the 3 categories were FATS, HATS and AFREGS) into linear regression models or by stratifying on the study indicator in Cox regression models. Results are presented separately for each study and as well as for the 3 studies combined. To adjust for the differential duration of the studies (2.5 years for FATS, 3 years for HATS and AFREGS) changes in % stenosis ($\Delta\%S_{\text{prox}}$) were tri-annualized.

Associations between patient characteristics and the MS were tested using logistic regression. ANOVA and linear regression were used to test associations with coronary disease progression. Outliers were detected using the value of studentized residuals and Bonferonni correction and were excluded from the comparison. Cox proportional hazards model was used to test association with the risk of CV events. Kaplan-Meier curves were compared to describe the accumulation of CV events in groups over time and survival curves were compared using the log-rank test. All Cox models and log-rank tests used stratification on the study. Multivariate models for disease progression and for CV events were developed in the framework of linear regression and Cox regression, respectively, using the forward selection method ($p < 0.05$ for inclusion). In addition, we tried backward elimination ($p > 0.05$ for exclusion) to see if there are any alternative models. Factors that were considered for inclusion in the multivariate model were: MS, therapy, therapy related variables (% change in LDL-C and % change in HDL-C) and baseline variables that were not significantly related to MS.

To examine the association between rapid (upper quartile) disease progression and CV events independent of other available risk factors for events, disease progression (as $\Delta\%S_{\text{prox}} \geq 3\%$ vs. $< 3\%$) was added into the final multivariate model for CV events. Due to a number of missing

values for some of the variables in the multivariate models, we applied a standard technique for multiple imputation of missing data using a sequence of regression models. (8,9)

RESULTS

As described in Table 2, the 233 patients with the MS in the combined dataset were older (55 vs. 53 years, $p=0.001$), with a higher proportion of females (12 vs. 2%, $p<0.001$) and a higher BMI (mean 29 vs. 26 kg/m², $p<0.001$) than the 212 patients without. As expected, a greater proportion of patients with history of CAD, hypertension or diabetes mellitus were found in the MS group. The subjects with the MS had higher levels of triglycerides (mean 241 vs. 150 mg/dl, $p<0.001$), fasting glucose (mean 99 vs. 85 mg dl, $p<0.001$), and insulin (mean 24 vs. 16 μ U/dl, $p<0.001$). They had lower levels of LDL-C (mean 131 vs. 154 mg/dl, $p<0.001$) and HDL-C (mean 32 vs. 36 mg/dl, $p<0.001$). Furthermore, the subjects with the MS had more severe mean coronary stenosis (mean %S_{prox}=39 vs. 36%; $p=0.003$) at baseline.

Most of the above mentioned differences in patient characteristics between those with and without the MS were consistent across the 3 studies. However for a few characteristics these differences were not consistent. Patients with and without the MS had similar prevalence of history of MI in HATS. But history of MI was more frequent among those without the MS (53%) than among those with it (33%) in AFREGS. While we found that in HATS and AFREGS those with the MS tended to have higher levels of total cholesterol compared to those without, the trend was opposite in FATS. Similarly, in HATS mean ApoA1 values were higher among those with the MS than those without, but the trend was opposite in FATS. The higher level of insulin in those with the MS was more pronounced in HATS than in AFREGS.

As presented in Figure 1, over 3 years, patients with the MS had significantly greater coronary stenosis progression compared to those without; Δ %S_{prox}=2.9 vs. 2.0 for those receiving placebo and 0.5 vs. -0.3 for those receiving active treatment ($p=0.04$ for the MS and $p<0.001$ for therapy). The interaction between therapy and the MS status was not statistically significant ($p=0.4$) suggesting comparable relative benefits from therapy, independent of the MS status. Six outliers in stenosis progression were detected and were excluded from all univariate analyses. Inclusion of the 6 outliers did not alter the conclusions with the exception of the effect of the MS that was still substantial but not statistical significant. Subset analyses have also shown that the conclusions are consistent across the 3 studies.

Furthermore, multivariate analysis showed that the intervention with lipid therapies used in these 3 studies was significantly and independently associated with improvement of coronary stenosis severity. The variables that were considered for inclusion into the multivariate analysis to predict stenosis progression were: presence of the MS, lipid therapy, change in HDL-C, change in LDL-C, history of MI, current smoking, ApoB and ApoA1. Total cholesterol was not included as a covariate because its components (triglycerides and HDL-C) are related to the MS. After adjustment for the study effect, 2 variables were selected into the multivariate model: lipid therapy and presence of the MS. Outliers were excluded from the multivariate model. The average difference in the in-trial mean coronary stenosis change between those with and without lipid therapy, estimated from the multivariate model, was Δ %S_{prox}=-2.27 (95% CI: -3.313, -1.41, $p<0.001$). In the multivariate model the presence of the MS was significantly associated with coronary stenosis progression with a mean increase of Δ %S_{prox}=0.79% compared to subjects without the MS (95% CI: 0.01, 1.57%, $p=0.048$). When outliers were included in the multivariate model, the only variable selected into the model was lipid therapy (mean difference of -2.51 between subjects with and without the therapy).

Overall there were 67 (15%) primary CV events including 6 (1.3%) CV deaths, 27 (6%) nonfatal MI, 7 (1.6%) ischemic strokes, and 27 (6%) revascularizations for progressive ischemia. The primary event was the one of these that occurred first.

As shown in Figure 2, patients with the MS had a higher rate of the composite of major CV events than those without (28 vs. 17% at 3 years for those receiving placebo and 13 vs. 3% at 3 years for those treated, overall $p=0.01$). The lipid therapy effectively reduced the major event rate for patients with the MS (13 vs. 28% at 3 years, $p=0.03$) and those without (3 vs. 17% at 3 years, $p=0.002$). Similar differences were seen when the data were analyzed by study.

As shown in Figure 3, more rapid coronary stenosis progression ($\Delta\%S_{\text{prox}}$ grouped by quartiles) was significantly associated with increased risk of major CV events ($p<0.001$ for trend). This trend was particularly driven by subjects in the highest group of $\Delta\%S_{\text{prox}}$ ($\geq 3\%$ over 3 years) where the event rate was substantially higher than in the other three groups. We observed the same association for subjects with and without the MS (trends in both groups were statistically significant) and for each study (trends were statistically significant in all 3 studies).

Multivariate analysis for CV events provided further evidence for the effect of more rapid coronary stenosis progression (defined as $\Delta\%S_{\text{prox}} \geq 3\%$) on the CV event rate. The same covariates used in the multivariate analysis for stenosis change were considered for this analysis to predict CV events. Variables selected into the multivariate model for CV events were: lipid therapy, history of MI, presence of MS and total cholesterol. Stenosis progression ($\Delta\%S_{\text{prox}} \geq 3$ vs. <3) was then added into the model. As shown in Table 3, in the multivariate analysis, stenosis progression $\geq 3.0\%S_{\text{prox}}$ was significantly and independently associated with 3.5-fold increased event risk (HR=3.54, 95% CI: 2.07–6.04, $p<0.001$). Lipid therapy was associated with 44% lower event risk compared to no therapy (HR=0.56, 95% CI: 0.32–0.97, $p=0.04$). Patients with history of MI had a 3-fold increased risk of the event compared to those without (HR=3.03, 95% CI: 1.65–5.57, $p<0.001$). Presence of the MS was associated with almost 2-fold increase in the event risk (HR=1.87, 95% CI: 1.07–3.26, $p=0.03$).

The linear regression analysis for the association of LDL-C-lowering and HDL-C-raising (both as continuous variables) with $\Delta\%S_{\text{prox}}$ shown in Table 4 revealed that, on the average, each 10% of LDL-C-lowering or 10% of HDL-C-raising was associated with a mean $\Delta\%S_{\text{prox}}$ of $-0.3\%S$. When LDL-C-lowering and HDL-C-raising were adjusted for each other in the model 3, the associations between the % lipid change and $\Delta\%S_{\text{prox}}$ remained statistically significant ($p<0.001$ for % LDL-C-lowering and $p=0.02$ for % HDL-C-raising) with only slightly reduced coefficients. The interaction of LDL-C-lowering and HDL-C-raising with the study was not statistically significant.

As described in Table 5, the Cox regression analysis showed that each 10% LDL-C-lowering was associated with 11% event risk reduction (HR=0.89, 95% CI: 0.81–0.98, $p=0.02$). Each 10% HDL-C-raising was associated with 22% event risk reduction (HR=0.78, 95% CI: 0.68–0.90, $p<0.001$). When LDL-C-lowering and HDL-C-raising were adjusted for each other in the model 3, the associations between the % lipid change and risk of event had similar hazard ratios as in the unadjusted models 1 and 2. While HDL-C-raising remained statistically significant in model 3 ($p=0.002$), LDL-C-lowering had a non-significant trend ($p=0.11$). The interaction of LDL-C-lowering and HDL-C-raising with the study was not statistically significant.

DISCUSSIONS

The MS (4) is a constellation of atherogenic risk factors that result in an increased risk for CV disease and events. In this combined analysis of 3 angiographic trials, patients with the MS were more likely to have clinically established CAD and more severe coronary stenosis at

baseline than those without despite the differences in other risk factors. Although the increased CV risk in patients with the MS is well established (10,11), the current analysis provides quantitative assessment of coronary stenosis progression in this population. We found that patients with the MS had more rapid disease progression and experienced higher rates of major CV events that were independently predicted by history of myocardial infarction, presence of the MS and greater ($\geq 3\%$ S) coronary stenosis progression.

Furthermore, despite the known limitations of quantitative coronary angiography in reliable identification of the plaque stability or vulnerability (12), mean proximal coronary disease progression by 3% stenosis or more over 3 years was significantly and independently associated with 3.5-fold increased event risk ($p < 0.001$). Thus, quantitatively measured coronary stenosis progression in treatment is strongly associated with in-treatment CV event rate, and also identifies subjects at significantly higher risk for future major events. (13,14)

The lipid profile of the MS is characterized by low levels of HDL-C, elevated triglycerides and small/dense LDL particles. (15) Therapy combining niacin or fibric acid derivatives with LDL-C-lowering agents such as statins, ezetimibe or resins should be ideal to correct all these lipid abnormalities. (16,17) This analysis, with the 3 studies used different drugs and had different achieved lipid response, demonstrated that intensive lipid-altering therapy targeting both LDL-C-lowering and HDL-C-raising, effectively decreased coronary stenosis progression in patients with the MS by 86% (from mean of 2.9% stenosis change to 0.5%, $p < 0.001$). The therapy also significantly reduced overall major CV event risk by 56% ($p = 0.03$ for those with the MS and $p = 0.002$ for those without). The present combined analysis is consistent with the CV event reduction seen with niacin in the Coronary Drug Project in post myocardial infarction patients. (18) Our analysis and the report on the MS patients in the Coronary Drug Project by Canner (19) extend these findings, demonstrating greater clinical benefit when HDL-C-raising is combined with LDL-C-lowering in patients with the MS. The greater CV event risk reduction with LDL-C-lowering plus HDL-C-raising is supported by the epidemiologic studies. (20)

There remain unanswered questions regarding how aggressively to treat the dyslipidemia of the MS. Currently, MS is not considered as a coronary disease risk equivalent and thus no specific guidelines are available for goal LDL-C or HDL-C levels in this patient population. (21) The current multivariate analysis provides insight into this question by demonstrating the independent contributions of LDL-C-lowering alone, HDL-C-raising alone, or of LDL-C-lowering plus HDL-C-raising on coronary stenosis progression and CV event risk. On average, during 3 years treatment, each 10% LDL-C reduction decreased mean stenosis by 0.3% ($p < 0.001$) and reduced clinical event risk by 11% ($p = 0.02$). Similarly, each 10% HDL-C increase was associated with an average 0.3%S decreased ($p = 0.02$) and 22% reduction in clinical events ($p < 0.001$). These angiographic and clinical benefits from LDL-C-lowering and HDL-C-raising are independent and consistent with that seen in meta-regression analyses of lipid therapy in large populations with, or at risk for, CV disease. (22,23) Results from this analysis provided further evidence supporting the utilization of combination lipid therapy aiming at LDL-C-lowering plus HDL-C-raising, specifically in patients with the MS.

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Figure 1.

Mean coronary artery percent stenosis change by the MS and therapy. Patients with the MS had more rapid coronary stenosis progression than those without: 2.9 vs. 2.0% stenosis for those not receiving therapy and 0.5 vs. -0.3% stenosis for those receiving therapy, overall $p=0.02$ after adjustment for treatment. The lipid therapy significantly decreased stenosis progression in patients with the MS (0.5 vs. 2.9% stenosis, $p<0.001$) and induced regression in those without (-0.3 vs. 2.0% stenosis, $p<0.001$).

Figure 2.

Kaplan-Meier curves of CV event free survival by MS and therapy. Patients with the MS had a higher rate of composite major CV events than those without: 28 vs. 17% for those not receiving therapy and 13 vs. 3% for those receiving therapy, overall $p=0.01$. The lipid therapy significantly reduced the event rate in both patients with the MS (13 vs. 28%, $p=0.03$) and without (3 vs. 17%, $p=0.002$).

Figure 3.

The association between coronary stenosis progression in quartiles and CV event rate for all subjects who completed their final angiography and for those with and without the MS was statistically significant ($p < 0.001$). This trend is particularly driven by subjects in the highest quartile of percent stenosis change with $\geq 3\%$.

Table 1

Summary of patient characteristics, study designed therapy, lipid response, and endpoints in FATS, HATS, and AFREGS

Variable	FATS	HATS	AFREGS
Number of subjects completing both baseline and final angiograms	n=120	n=146	n=130
Study duration, years (period)	2.5 (1983–89)	3 (1993–2000)	3 (1993–1996)
Patient population	FH CAD & ↑apoB	CAD & ↓HDL	CAD & ↓HDL
Male **	100%	87%	92%
Age (years), mean±SD **	46±9	53±8	63±7
Metabolic Syndrome (+) **	42%	66%	47%
Body Mass Index (BMI) (Kg/m ²), mean±SD **	27±4	29±4	26±4
Clinically established CHD **	NA	77%	65%
History of myocardial infarction **	NA	55%	43%
Hypertension **	NA	49%	71%
Diabetes mellitus [#] **	4%	13%	0%
Current smoking **	NA	47%	8%
Total cholesterol (mg/dl), mean±SD **	270±43	197±31	196±31
Triglycerides (mg/dl), mean±SD **	204±125	217±104	168±81
LDL-C (mg/dl), mean±SD **	189±48	113±30	128±26
HDL-C (mg/dl), mean±SD **	38±8	31±5	34±6
ApoB (mg/dl), mean±SD **	156±25	116±22	NA
ApoA1 (mg/dl), mean±SD **	130±15	109±14	NA
Fasting glucose (mg/dl), mean±SD **	93±17	102±29	82±14
Insulin level (μU/dl), mean±SD **	NA	24±13	16±18
Coronary disease severity, mean %S _{prox} mean±SD **	33±12	35±10	46±9
Control regimen	Diet±C *	Diet, Exercise	Diet, Exercise
Study therapy	L+C N+C	S+N±V+Exercise	G+C+N+Exercise
Change in LDL-C [†] by study Rx	−46% −32%	−43%	−22%
Change in HDL-C [†] by study Rx	+15% +43%	+29%	+36%
Δ%S _{prox} by QCA, Control/Rx	+2.1/−0.9 +2.1/−0.7	+2.8/+0.2	+1.4/−0.8
Event risk reduction (ITT)	66% 78%	61%	53%

FH CAD = positive family history of clinical coronary disease

* patients with LDL-C >90th percentile received colestipol

** statistically significant difference among the three studies

[#]Patients with diabetes were excluded from FATS

[†]from baseline levels

L=Lovastatin, C=Colestipol, N=Niacin, S=Simvastatin, Vit.=Vitamins, G=Gemfibrozil.

ITT = intention-to-treat analysis

Comparison of baseline characteristics between patients with and without metabolic syndrome (MS) in combined patient data from FATS, HATS and AFREGS.

Table 2

Characteristic	All 3 studies					FATS		HATS		AFREGS		p-value**
	N	MS (+)	MS (-)	p-value*	MS (+)	MS (-)	MS (+)	MS (-)	MS (+)	MS (-)	MS (-)	
Number of patients	n=233	n=212	n=82	n=60	n=82	n=54	n=106	n=54	n=67	n=76	n=76	
Age (years), mean±SD	445	55±10	53±11	0.01	48±8	45±9	54±8	52±9	64±8	63±7	63±7	0.9
Male Gender	445	88%	98%	<0.001	100%	100%	84%	94%	85%	99%	99%	0.2
BMI (Kg/m ²), mean±SD	445	29±4	26±3	<0.001	29±4	25±3	30±4	26±3	28±4	25±3	25±3	0.4
Clinically established CAD	303	79%	62%	0.004	--	--	83%	65%	72%	59%	59%	0.4
Prior myocardial infarction	303	47%	52%	0.2	--	--	57%	52%	33%	53%	53%	0.04
Hypertension	303	72%	42%	<0.001	--	--	63%	20%	87%	58%	58%	0.5
Diabetes mellitus#	442	10%	1%	<0.001	7%	1%	18%	2%	0%	0%	0%	0.6
Current smoking	302	33%	23%	0.7	--	--	50%	41%	6%	11%	11%	0.2
Total cholesterol (mg/dl), mean±SD	445	217±44	224±55	0.4	265±38	274±47	198±32	194±30	203±29	190±31	190±31	0.03
Triglycerides (mg/dl), mean±SD	444	241±107	150±83	<0.001	265±135	160±96	246±103	160±80	210±77	131±65	131±65	0.08
LDL-C (mg/dl), mean±SD	445	131±42	154±52	<0.001	176±42	199±49	108±27	123±33	128±27	129±26	129±26	0.2
HDL-C (mg/dl), mean±SD	445	32±5	36±8	<0.001	34±4	41±9	31±5	32±4	33±5	35±6	35±6	0.12
ApoB (mg/dl), mean±SD	301	131±29	139±33	0.7	156±22	156±28	116±22	114±22	--	--	--	0.6
ApoA1 (mg/dl), mean±SD	301	116±16	122±20	0.7	127±13	133±16	110±15	106±13	--	--	--	0.005
Fasting glucose (mg/dl), mean±SD	442	99±27	85±15	<0.001	98±16	89±17	108±33	91±11	87±14	77±12	77±12	0.7
Insulin level (μU/dl), mean±SD	287	24±16	16±15	<0.001	--	--	27±13	18±10	18±18	14±18	14±18	0.003
Coronary disease severity, mean %S _{prox} , mean±SD	415	39±12	36±12	0.003	35±12	32±12	37±11	32±9	47±10	45±8	45±8	0.4

* Logistic regression of metabolic syndrome, (+) vs., (-), on the characteristic with adjustment for the study effect

** P-value for the interaction between the characteristic and study from the logistic regression of metabolic syndrome on the characteristic, the study effect and the interaction between the characteristic and study. This p-value tests whether the difference in characteristics between those with and without metabolic syndrome varies across the three studies.

Patients with diabetes at baseline were excluded from FATS.

Table 3

Multivariate analysis for major cardiovascular events

Variables	Hazard Ratio (95% CI)	p-value
Stenosis progression $\geq 3.0\% S_{\text{prox}}$ over 3 years	3.54 (2.07 – 6.04)	<0.001
Lipid therapy	0.56 (0.32 – 0.97)	0.04
History of myocardial infarction	3.03 (1.65 – 5.57)	<0.001
Presence of metabolic syndrome	1.87 (1.07 – 3.26)	0.03

Association of low-density lipoprotein cholesterol (LDL-C)-lowering and high density lipoprotein cholesterol (HDL-C)-raising with coronary stenosis severity change. Univariate (models 1 and 2) and multivariate (model 3) linear regression.

Table 4

Model	Change in % stenosis ($\Delta\%$ S)					
	All 3 studies N=445	FATS N=120	HATS N=146	AFREGS N=130	Interaction with study	p-value
	Regr. Coef. (95% CI)	p-value	Regr. Coef. (95% CI)	Regr. Coef. (95% CI)	Regr. Coef. (95% CI)	
1. LDL-C-lowering (per 10%)	-0.34 (-0.49 – -0.18)	<0.001	-0.60 (-0.97 – -0.23)	-0.23 (-0.47 – 0.01)	-0.24 (-0.45 – -0.03)	0.3
2. HDL-C-raising (per 10%)	-0.29 (-0.46 – -0.12)	<0.001	-0.60 (-1.02 – -0.18)	-0.35 (-0.71 – 0.00)	-0.11 (-0.30 – 0.07)	0.3
3. LDL-C-lowering (per 10%)	-0.29 (-0.45 – -0.13)	<0.001	-0.55 (-0.95 – -0.16)	-0.18 (-0.42 – 0.07)	-0.22 (-0.44 – 0.00)	0.6
HDL-C-raising (per 10%)	-0.21 (-0.39 – -0.04)	0.02	-0.48 (-0.90 – -0.06)	-0.29 (-0.66 – 0.08)	-0.05 (-0.25 – 0.14)	0.3

Outliers excluded: 5 for models including data from all three studies (including testing for interaction with study), no outliers for FATS (except for LDL model with one outlier), one outlier for HATS, 3 outliers for AFREGS

* Adjusted for the study effect.

** Interaction of the predictor with the study variable (ANOVA)

Table 5

Cox regression analysis of major cardiovascular event rate with stratification on the study.

Model	Cardiovascular event risk					
	All 3 studies N=413		FATS N=120	HATS N=154	AFREGS N=139	Interaction with study [*]
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	p-value
1. LDL-C-lowering (per 10%)	0.89 (0.81 – 0.98)	0.02	0.78 (0.63 – 0.98)	0.95 (0.81 – 1.11)	0.89 (0.77 – 1.03)	0.2
2. HDL-C-raising (per 10%)	0.78 (0.68 – 0.90)	<0.001	0.67 (0.44 – 1.00)	0.76 (0.57 – 1.01)	0.81 (0.69 – 0.96)	0.7
3. LDL-C-lowering (per 10%)	0.92 (0.83 – 1.02)	0.11	0.81 (0.64 – 1.03)	0.97 (0.82 – 1.15)	0.93 (0.79 – 1.08)	0.3
HDL-C-raising (per 10%)	0.80 (0.69 – 0.92)	0.002	0.70 (0.47 – 1.06)	0.78 (0.57 – 1.05)	0.83 (0.70 – 0.98)	0.8

^{*} interaction of the predictor with the study variable (likelihood ratio test)