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SIMVASTATIN AND NIACIN, ANTIOXIDANT VITAMINS, OR THE COMBINATION FOR THE PREVENTION OF CORONARY DISEASE

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ABSTRACT

Background Both lipid-modifying therapy and antioxidant vitamins are thought to have benefit in patients with coronary disease. We studied simvastatin–niacin and antioxidant-vitamin therapy, alone and together, for cardiovascular protection in patients with coronary disease and low plasma levels of high-density lipoprotein (HDL) cholesterol.

Methods In a three-year, double-blind trial, 160 patients with coronary disease, low HDL cholesterol levels, and normal low-density lipoprotein (LDL) cholesterol levels were randomly assigned to receive one of four regimens: simvastatin plus niacin, antioxidants, simvastatin–niacin plus antioxidants, or placebos. The end points were arteriographic evidence of a change in coronary stenosis and the occurrence of a first cardiovascular event (death, myocardial infarction, stroke, or revascularization).

Results The mean levels of LDL and HDL cholesterol were unaltered in the antioxidant group and the placebo group; these levels changed substantially (by −42 percent and +26 percent, respectively) in the simvastatin–niacin group. The protective increase in HDL2 with simvastatin plus niacin was attenuated by concurrent therapy with antioxidants. The average stenosis progressed by 3.9 percent with placebos, 1.8 percent with antioxidants ($P=0.16$ for the comparison with the placebo group), and 0.7 percent with simvastatin–niacin plus antioxidants ($P=0.004$) and regressed by 0.4 percent with simvastatin–niacin alone ($P<0.001$). The frequency of the clinical end point was 24 percent with placebos, 3 percent with simvastatin–niacin alone, 21 percent in the antioxidant-therapy group, and 14 percent in the group given simvastatin–niacin plus antioxidants.

Conclusions Simvastatin plus niacin provides marked clinical and angiographically measurable benefits in patients with coronary disease and low HDL levels. The use of antioxidant vitamins in this setting must be questioned. (N Engl J Med 2001;345:1583-92.)

ON the basis of epidemiologic data, it has been predicted[1,2] that each 1 percent reduction in the level of low-density lipoprotein (LDL) cholesterol results in a reduction of 1.0 to 1.5 percent in the risk of major cardiovascular events. In trials of LDL-lowering strategies, a reduction of 12 to 38 percent in the LDL level has resulted in a relative reduction in risk of 19 to 35 percent.[3,4] Similarly, in an insightful epidemiologic analysis[5] of risk related to high-density lipoprotein (HDL) cholesterol, an increment of 1 mg per deciliter (0.03 mmol per liter or about 2 to 3 percent) in the HDL level has been associated with a reduction of 2 to 4 percent in the risk of cardiac events that is independent of the LDL level. If the benefits of raising the HDL level and lowering the LDL level are independent and of similar magnitude, as the results of several trials imply,[6-8] then simultaneous therapeutic alterations of 30 to 40 percent in the levels of these lipoproteins should theoretically reduce the risk of events by 60 to 80 percent. Furthermore, a low HDL level may reflect an antioxidant deficiency[9]; therefore, supplemental antioxidants may also reduce risk.[10] We undertook a trial to test the hypothesis that lipid-altering and antioxidant therapy provide independent and additive benefits for patients with coronary artery disease and low HDL levels.

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METHODS

Study Patients

The HDL-Atherosclerosis Treatment Study (HATS)[11] enrolled 160 men (younger than 63 years of age) and women (younger than 70 years of age) with clinical coronary disease (defined as previous myocardial infarction, coronary interventions, or confirmed angina) and with at least three stenoses of at least 30 percent of the luminal diameter or one stenosis of at least 50 percent. All had low levels of HDL cholesterol (35 mg per deciliter [0.91 mmol per liter] or lower in men and 40 mg per deciliter [1.03 mmol per liter] in women), LDL cholesterol levels of 145 mg per deciliter (3.75 mmol per liter) or lower, and triglyceride levels below 400 mg per deciliter (4.52 mmol per liter). Of 454 apparently eligible patients, 294 were not enrolled because they declined to participate; because screening for confirmation of eligibility found lipid levels outside of the specified ranges; because they had previously undergone coronary bypass surgery; or because they had severe hypertension, recent gout, or liver, thyroid, or kidney disease, or uncontrolled diabetes. Twenty-six patients in Canada and 134 patients in the Seattle area were enrolled between January 1995 and January 1997.

The patients and their physicians were informed that they would be blinded to the treatment-group assignment and would make all decisions about clinical care. At the time of enrollment, patients read, discussed, and signed a consent form that had been approved by the human-subjects committee at each center.

Patients were stratified according to sex, triglyceride level (above or below 200 mg per deciliter [2.26 mmol per liter]), and level of risk (two levels). Those who were currently smoking, who had diabetes, or whose LDL cholesterol level was higher than 130 were considered to be at higher risk.[12] All received counseling regarding changes in lifestyle that could increase their HDL cholesterol levels and underwent randomization within their risk stratum. The trial was double-blinded and fully placebo-controlled with a two-by-two factorial design; the four regimens were simvastatin plus niacin, antioxidant vitamins, simvastatin–niacin plus antioxidants, and all placebos.

Treatments

Simvastatin plus Niacin

We began simvastatin (Zocor, Merck, West Point, Pa.) therapy at 10 mg per day for patients with an LDL cholesterol level of 110 mg per deciliter (2.84 mmol per liter) or lower on screening and 20 mg per day for those with an LDL cholesterol level higher than 110 mg per deciliter. The dose was increased by 10 mg per day in patients whose LDL cholesterol level was higher than 90 mg per deciliter (2.33 mmol per liter) in any sample during the first year of the study and was reduced by 10 mg per day if the LDL cholesterol level fell below 40 mg per deciliter (1.03 mmol per liter) at any time during the study. During treatment, patients receiving the matching placebo were given 10 mg of simvastatin if their LDL cholesterol level was 140 mg per deciliter (3.62 mmol per liter) or higher; the target level was 130 mg per deciliter (3.37 mmol per liter) or lower. The dose of slow-release niacin (Slo-Niacin, Upsher–Smith, Minneapolis) was increased linearly from 250 mg twice daily to 1000 mg twice daily at four weeks. Patients whose HDL cholesterol levels had not increased by at least 5 mg per deciliter (0.13 mmol per liter) at 3 months, at least 8 mg per deciliter (0.21 mmol per liter) at 8 months, and at least 10 mg per deciliter at 12 months were switched to crystalline niacin (Niacor, Upsher–Smith), the dose of which was gradually increased to 3 g per day or, at most, 4 g per day in order to meet the target levels. Niacin "placebo" tablets (taken at a dose of 50 mg twice daily) were active, provoking flushing without affecting lipid levels.[13]

Antioxidant Vitamins

The antioxidants given twice daily included a total daily dose of 800 IU of vitamin E (as *d*-alpha-tocopherol), 1000 mg of vitamin C, 25 mg of natural beta carotene, and 100 μg of selenium. The gel capsules given as placebos were identical in appearance to the antioxidant-vitamin pills.

Counseling and Exercise Training to Raise the HDL Level

All patients received counseling[14] for 20 minutes during each visit, emphasizing weight loss and consumption of monounsaturated fats. Three-day records of food intake obtained at entry, at 12 months, and at 24 months were analyzed to determine calorie, cholesterol, fat, and vitamin intake.

For help with smoking cessation, patients were repeatedly encouraged to try free group counseling, nicotine patches, hypnosis, or a combination of these approaches. All patients were encouraged to enter a free, supervised, phase III rehabilitation program involving three hours per week of exercise for four months. The goals were to limit the heart rate to below the ischemic threshold,[15] to increase exercise capacity in a safe manner, and to encourage patients to continue to engage in regular exercise.

Clinic Visits and Laboratory Tests

Clinic visits took place monthly for the first five visits, then bimonthly until angiography was performed at three years. Treatment with the study drugs was then stopped, and a close-out clinic visit occurred two months later. Unused study drugs were returned and counted, new drug supplies and counseling regarding lifestyle changes were provided, and a directed interview and physical examination were performed. An additional physician who was aware of the treatment-group assignments monitored the laboratory results, spoke at least briefly with each patient, and spoke with patients at length if there were side effects that suggested the need for an adjustment in the doses. For patients with diabetes, glucometer results obtained at home were reviewed bimonthly by a nurse experienced with the management of diabetes.

The fasting plasma concentrations of triglycerides and total, HDL, and LDL cholesterol were determined every four months by Northwest Lipid Research Laboratories.[7,16] At base line, at one year, at two years, and two months after therapy ended, a more detailed analysis was conducted that included the levels of cholesterol and triglycerides contained in HDL2 and HDL3, and in very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and LDL separated by ultracentrifuge; levels of apolipoproteins B, A-I, A-II, and E; apolipoprotein E isoforms; and Lp(a) lipoprotein. At base line and at one year, HDL was freshly separated into lipoprotein particles containing only apolipoprotein A-I, commonly referred to as Lp(A-I), and those with both apolipoprotein A-I and apolipoprotein A-II, referred to as Lp(A-I, A-II). Both subpopulations were assayed to determine their composition and their particle-size distribution.[17] Samples obtained at base line and at one year and frozen (at −70°C) were tested to determine the level of apolipoprotein C-III[18] and the fractional esterification rate of HDL.[19] At appropriate intervals, uric acid, homocysteine, glucose, aspartate aminotransferase, creatine kinase, and fasting insulin levels were measured. Plasma levels of vitamins E and C and beta carotene were measured at base line, 12 months, and 24 months.[20] LDL was isolated, and its resistance to oxidative stress was measured.[21]

Arteriography

During catheterization at base line, eight views of the left and right coronary arteries were filmed after 0.2 to 0.4 mg of nitroglycerin had been administered sublingually[7]; this process was repeated for the follow-up angiogram. A detailed coronary map was drawn that included the locations of all lesions that caused stenosis of at least 15 percent of the luminal diameter. The fully blinded assessment of the extent of any change in stenosis has been described previously.[7,22] It took an average of 15 person-hours per pair of films to measure the change in disease.

The regions of the selected images showing the lesion of interest were optically magnified up to four times and digitally magnified two times with the use of a Sony SME 3500 digital cine projector linked to a PowerMac 7100 computer running a program containing the National Institutes of Health Image program; the meth-

ods used were developed and validated in our laboratory.[23] The selected initial and final images of lesions were measured side by side for consistency. For each lesion, the minimal luminal diameter (Dm) and nearby normal diameters (Dn) were measured, in millimeters, with the catheter used as a calibration standard. The two principal estimates of the severity of disease were Dm and the stenosis, expressed as a percentage, which was calculated as $100(1-[Dm \div Dn])$; these estimates for each of the 1812 lesions measured were averaged from two to six separate measurements from each film.[22]

Statistical Analysis

Differences among groups in base-line risk factors were compared by one-way analysis of variance or by Pearson's chi-square test.[24] The base-line lipid levels and those measured during the course of treatment were compared within groups by paired t-tests; differences among groups in the response of HDL2 to therapy were compared by the two-sample t-test.

The prespecified primary end point was the mean change per patient from the initial arteriogram to the final arteriogram in the percent stenosis caused by the most severe lesion in each of the nine proximal coronary segments (in the example in Fig. 1, the mean change in percent stenosis in proximal lesions is 4.0). The results of the formal test for therapy interaction (deviation from the factorial-design assumptions of independent and additive effects of each of the two therapies) were significant for this end point and remained so after statistical adjustment for minor imbalances in base-line risk. Our a priori contingency plan in this event was to replace the planned factorial analysis with the more informative Bonferroni–Dunn[24] statistical comparison of each active treatment group with the placebo group. A P value of less than 0.05 was considered to indicate statistical significance. Secondary end points included the mean change in percent stenosis in lesions of varying degrees of severity and the mean change in luminal diameter in proximal lesions and all lesions. We examined 48 candidate risk variables for correlation with the change in the severity of proximal stenosis, using univariate Pearson's correlations or, if appropriate, Spearman correlations.[24]

The prespecified primary clinical end point, analyzed according to the intention-to-treat principle for all 160 patients, was the time to the first of the following events: death from coronary causes, nonfatal myocardial infarction, stroke, or revascularization for worsening ischemia. The treatment groups were compared with the placebo group by Kaplan–Meier and Cox proportional-hazards techniques[24]; in subgroup analyses of events, we used Fisher's exact test with Bonferroni's adjustments.[24]

RESULTS

Base-Line Characteristics

The average age of the patients was 53 years; 13 percent of the 160 patients were female; 49 percent had received a diagnosis of hypertension; 46 percent were former smokers and 24 percent were current smokers; 55 percent had previously had a myocardial infarction; 49 percent had previously undergone angioplasty; and 16 percent had diagnosed diabetes. The distribution of these variables plus the body-mass index (defined

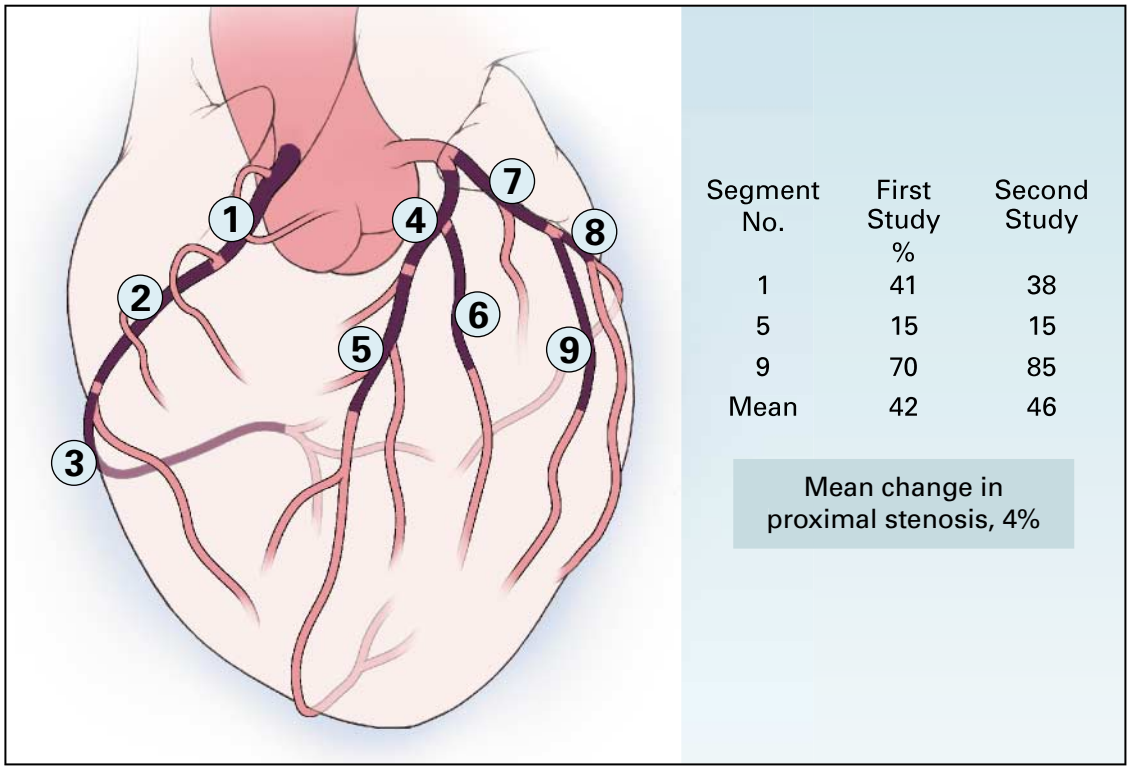

Figure 1. Location of Nine Standard Proximal Segments of the Coronary Anatomy.

The lesion causing the most severe stenosis in each of these nine segments was measured in each patient. The mean change in the severity of proximal stenosis (expressed as a percentage) between the two studies in this patient was 4 percent. Although a lesion in each of the nine segments was measured, only the measurements for segments 1, 5, and 9 are given.

as the weight in kilograms divided by the square of the height in meters; mean, 29), the Framingham risk score[12] (mean, 1.3 percent per year), and the mean severity of proximal stenosis at base line (mean, 34.9 percent) indicated that randomization had produced groups that were very well balanced. Diabetes was more prevalent in the group assigned to simvastatin–niacin plus antioxidants and somewhat less prevalent in the simvastatin–niacin group (P=0.04). A total of 146 patients (91 percent) completed the angiographic protocol. Two patients died, and 12 withdrew from the study (2 of them because of niacin intolerance) after a mean (±SD) of 14±11 months.

Drug Compliance, Side Effects, and Dietary Changes

Because of titration to approach target levels, the recommended daily doses of study drugs varied from patient to patient. Compliance with the study regimens, measured by means of pill counts, ranged between 80 percent and 95 percent (Table 1). The mean doses of simvastatin and niacin taken by patients were 13±6 mg per day and 2.4±2.0 g per day, respectively.

Simvastatin plus niacin caused small but consistent increases in the levels of aspartate aminotransferase, creatine kinase, uric acid, homocysteine, and insulin, but not glucose (Table 1). Doses were reduced because of side effects no more frequently in the groups receiving active simvastatin–niacin therapy than in those receiving matching placebos. Reports of flushing were as frequent among those receiving active niacin as among those receiving its active matched placebo (30 percent vs. 23 percent; P=0.35); of 80 patients who were receiving active niacin, 2 withdrew from the study because of flushing and 2 remained in the study but stopped taking niacin.[25]

Dietary counseling did not alter the already low mean calorie, cholesterol, or fat intake (Table 1). The average dietary vitamin intake was 7.8 IU per day of E, 110 mg of C, and 3.5 mg of beta carotene.

Lipid, Lipoprotein, and Apolipoprotein Levels

Antioxidants did not affect lipid levels (Table 2), except for the level of HDL2 (considered to be the most protective component of HDL), which was lowered by 15 percent in the group that received only antioxidants (P=0.05 for the comparison with the pla-

TABLE 1. COMPLIANCE WITH STUDY REGIMENS AND CHANGE IN DIETARY FACTORS, VITAMIN INTAKE, WEIGHT, AND BLOOD PRESSURE AMONG THE 146 PATIENTS WHO COMPLETED THE COURSE OF TREATMENT.*

VARIABLE	PLACEBOS (N=34)		SIMVASTATIN–NIACIN (N=33)		ANTIOXIDANT VITAMINS (N=39)		SIMVASTATIN–NIACIN PLUS ANTIOXIDANTS (N=40)	
	AT BASE LINE	DURING THERAPY	AT BASE LINE	DURING THERAPY	AT BASE LINE	DURING THERAPY	AT BASE LINE	DURING THERAPY
Compliance (%)†								
Niacin	—	80	—	80	—	86	—	83
Simvastatin	—	88	—	89	—	90	—	92
Vitamins	—	88	—	93	—	93	—	95
Mean dietary intake‡								
Cholesterol (mg/day)	214	217	212	205	207	192	184	187
Calories (kcal/day)	1886	1867	1900	1897	1779	1713	1995	1826
Saturated fat (g/day)	19	18	18	17	15	14	17	17
Monounsaturated fat (g/day)	22	22	20	22	20	19	21	21
Ratio of polyunsaturated to saturated fat	0.7	0.7	0.7	0.8	0.8	0.8	0.8	0.8
Weight (kg)	92.1	93.3	91.0	91.3	89.9	91.5§	93.1	93.7
Blood pressure (mm Hg)	125/80	127/80	124/78	125/77	128/82	132/81	130/81	129/79¶
Laboratory variables								
Aspartate aminotransferase (U/liter)	22	24	23	29§	23	22	22	27§
Creatine kinase (U/liter)	76	86	78	96¶	83	81	67	80§
Uric acid (mg/dl)	6.2	6.2	5.8	6.3‖	5.8	5.5¶	5.7	5.9
Glucose (mg/dl)	98	99	102	105	104	104	106	109
Insulin (μU/ml)**	24	26	26	31	21	24	25	30‖
Homocysteine (μmol/liter)	9.1	7.6¶	8.5	9.4	8.5	8.1	8.1	9.9¶

*All differences within treatment groups between the base-line values and the values during therapy were nonsignificant unless otherwise indicated. There were no significant differences in base-line values between groups.

†Compliance was determined by pill counts, and percentages were averaged over the treatment period.

‡Data are from analysis of the 3-day food record obtained at base line and at 12 and 24 months during therapy. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

§P<0.005.

¶P<0.05.

‖P<0.01.

**To convert values to picomoles per liter, multiply by 6.0.

cebo group); antioxidants interacted adversely with simvastatin–niacin. The base-line levels of LDL cholesterol and triglycerides averaged 125 mg per deciliter and 213 mg per deciliter, respectively; the levels decreased by 42 percent and 36 percent, respectively, with simvastatin–niacin therapy alone and decreased similarly when antioxidants were added to the regimen. The HDL level averaged 31 mg per deciliter in the overall population; it increased by 26 percent in those treated with simvastatin–niacin alone and by 18 percent with added antioxidants (P=0.05). With simvastatin–niacin therapy alone, the levels of HDL2 and Lp(A-I) increased by 65 percent and 81 percent,[26] respectively. These responses were specifically blunted when antioxidants were added to the regimen (increases of 28 percent [P=0.02 for the comparison with the simvastatin–niacin group] and 28 percent [P=0.01],[26] respectively) — a predictable detrimental effect.[27,28] The levels and composition of Lp(A-I, A-II) were not altered by simvastatin–niacin therapy, antioxidants, or the combination of the two.[26]

Vitamin Levels and Resistance of LDL to Oxidation

Plasma vitamin concentrations increased significantly in 75 patients who received active vitamin therapy. The plasma vitamin E concentration increased from a mean of 15.0 mg per liter at base line to a mean of 28.1 mg per liter during treatment (P<0.001); the plasma vitamin C concentration increased from a mean of 0.6 mg per deciliter to 1.1 mg per deciliter (P<0.001); and the plasma concentration of beta carotene increased from a mean of 176 μg per liter to a mean of 849 μg per liter (P<0.001). Diene lag time,[21] an index of the resistance of LDL to oxidation, increased by 35 percent, from 52.4 minutes to 70.5 minutes (P<0.001).

TABLE 2. MEAN LIPID AND LIPOPROTEIN LEVELS BEFORE AND DURING THERAPY, ACCORDING TO TREATMENT GROUP AMONG PATIENTS WHO COMPLETED THE COURSE OF TREATMENT.*

MEASURE	PLACEBOS (N=34)		SIMVASTATIN–NIACIN (N=33)		ANTIOXIDANT VITAMINS (N=39)		SIMVASTATIN–NIACIN PLUS ANTIOXIDANTS (N=40)	
	AT BASE LINE	DURING THERAPY	AT BASE LINE	DURING THERAPY	AT BASE LINE	DURING THERAPY	AT BASE LINE	DURING THERAPY
Cholesterol (mg/dl)†								
Total	199	188‡	201	139§	189	189	199	146§
VLDL	40	37	38	23§	39	43	43	31§
LDL	127	116§	132	75§	117	112	124	79§
IDL	14.7	11‡	14	6§	13	11	15	6§
HDL	32	34‡	31	40§	32	33	30	36§
HDL2	3.9	3.8	3.8	6.1§	3.9	3.3¶	3.9	4.5
Triglycerides (mg/dl)‖								
Total	203	196	202	126§	207**	238**	236	164§
IDL	9.7	7.0¶	9.3	6.2‡	9.3	9.1	10.3	5.9§
HDL	15.3	13.3¶	13.8	11.7‡	14.2	15.1	15.6	12.9‡
Other lipoproteins (mg/dl)								
Lp(a) lipoprotein	30	29	27	23§	21	21	30	23
Apolipoproteins (mg/dl)								
B	117.6	104§	118	73§	109	108	119	79§
A-I	110.7	115	108	123§	110	116‡	109	121§
A-II	30	30	29	28	29	30	30	30
E	4.8	4.4	4.6	3.0§	4.9	5.3	5.2	3.8§
C-III (in apolipoprotein B particles)	5.6	5.5	5.3	3.4§	5.6	6.6	6.0	4.3§

*For total, LDL, and HDL cholesterol, and total triglycerides, the estimates of base-line levels are the averages of the base-line measurement and the second screening measurement. All estimates of levels during therapy are the averages of all measurements obtained during therapy. Differences within treatment groups between base-line values and the values during therapy were nonsignificant by the paired t-test unless otherwise indicated. P values have not been adjusted for multiple comparisons. VLDL denotes very-low-density lipoprotein, LDL low-density lipoprotein, IDL intermediate-density lipoprotein, and HDL high-density lipoprotein.

†To convert values to millimoles per liter, multiply by 0.02586.

‡P<0.01.

§P<0.001.

¶P<0.05.

‖To convert values to millimoles per liter, multiply by 0.01129.

**In this group, there were two major outliers with regard to triglyceride levels during therapy; both patients had diabetes. If their triglyceride levels are removed from the analyses, the mean base-line level becomes 204 mg per deciliter (2.30 mmol per liter), and the mean level during therapy becomes 205 mg per deciliter (2.31 mmol per liter).

Changes in the Severity of Proximal Stenosis

On average, after three years of placebo therapy, the mean percent stenosis in proximal arteries increased by 3.9 percent (from 34.5 percent) (Table 3). By contrast, the mean percent stenosis increased by 1.8 percent (Bonferroni-adjusted P=0.16 for the comparison with the placebo group) after antioxidant therapy, and decreased by 0.4 percent (P<0.001) after simvastatin–niacin therapy. With simvastatin–niacin plus antioxidants, proximal stenosis increased by 0.7 percent (P=0.004). Adjustment of this analysis for the base-line imbalance in the prevalence of diabetes had only minor, nonsignificant effects.

In a worst-case approach,[7] we assigned to all 14 patients without a final angiogram a value of 3.9 percent (the mean in the placebo group) for the increase in proximal stenosis. This worst-case assumption had no effect on the outcome (Table 3).

Analyses of Secondary Stenosis End Points

Table 3 shows the effect of treatment on certain subcategories of lesions, including all stenotic lesions measured in each patient, clinically significant stenosis (stenosis of 50 percent or more of the luminal diameter at base line), subclinical stenosis (30 to 49 percent of the luminal diameter), or minimal stenosis (less than 30 percent of the luminal diameter). In general, the treatment effects observed with respect to the primary angiographic end point were confirmed for the various subcategories of stenosis and were supported by the results for the mean minimal luminal diameter.

Correlates of Change in Proximal Stenosis

The variables measured during treatment that demonstrated the greatest univariate correlation with the mean change in the severity of proximal stenosis included the ratio of apolipoprotein C-III in non-HDL particles to that in HDL particles (r=0.34, P<0.001); the apolipoprotein A-I content of medium-sized or large (8.2 to 11.2 nm) Lp(A-I) particles (r=−0.32, P<0.001); the fractional esterification rate of HDL (r=0.31, P<0.001); the levels of apolipoprotein E (r=0.25, P=0.003), apolipoprotein B (r=0.22, P=0.007), LDL cholesterol (r=0.22, P=0.008), IDL cholesterol (r=0.20, P=0.02), VLDL cholesterol (r=0.19, P=0.02), HDL2 (r=−0.18, P=0.03), and fi-

TABLE 3. MEAN CHANGES, PER PATIENT, IN THE PERCENTAGE OF STENOSIS AND THE MINIMAL LUMINAL DIAMETER FOR NINE PROXIMAL LESIONS, FOR ALL LESIONS, AND FOR LESIONS IN VARIOUS CATEGORIES OF BASE-LINE SEVERITY, ACCORDING TO TREATMENT GROUP.*

MEASURE	NO. OF LESIONS†	PLACEBOS (N=34)	SIMVASTATIN–NIACIN (N=33)	ANTIOXIDANT VITAMINS (N=39)	SIMVASTATIN–NIACIN PLUS ANTIOXIDANTS (N=40)	OVERALL P VALUE†
Mean change in stenosis (percentage of diameter)‡						
Nine proximal lesions	1273	3.9±5.2	−0.4±2.8§	1.8±4.2	0.7±3.2¶	<0.001
Lesions in worst-case analysis‖		3.9±4.9	0.2±3.0§	1.9±4.1	0.9±3.2¶	<0.001
Lesions with ≥50% stenosis	226	0.1±7.8	−5.8±11.4	−3.5±12.9	0.5±6.4	0.09
Lesions with 30–49% stenosis	442	3.2±11.4	−0.8±3.6	0.7±7.7	0.8±5.0	0.20
Lesions with 0–29% stenosis	605	5.2±6.0	1.7±3.1¶	4.5±8.6	1.3±3.8¶	0.01
All lesions	1812	2.6±3.5	−0.3±2.1§	1.1±3.4	0.4±2.6¶	0.001
Lesions with ≥50% stenosis	274	0.3±7.1	−6.0±11.3	−3.5±12.8	0.4±6.2	0.06
Lesions with 30–49% stenosis	628	3.1±8.4	−1.0±3.1	−0.3±7.4	0.6±4.8	0.05
Lesions with 0–29% stenosis	910	4.0±4.6	1.2±2.8¶	3.7±7.7	1.4±3.0¶	0.03
Mean change in minimal luminal diameter (mm)						
Nine proximal lesions	1273	−0.14±0.20	−0.01±0.20**	−0.05±0.18††	0.01±0.19¶	0.006
All lesions	1812	−0.12±0.16	−0.01±0.20**	−0.03±0.15††	0.003±0.19¶	0.014

*The mean for each group (±SD) is based on the mean changes per patient in the various categories of lesions. Data have not been adjusted for multiple comparisons; the results for the primary end point (top row) that were obtained with the Bonferroni–Dunn adjustment for multiple comparisons are given in the text. With Bonferroni's adjustment, the P values for the comparisons between the active treatment groups and the placebo group are three times the unadjusted P values.

†Overall P values were calculated by a one-way analysis of variance.

‡The lesions in each category were approximately equally distributed among all four groups.

§Unadjusted P<0.001 by the pooled t-test for the comparison with the placebo group.

¶Unadjusted P<0.005 by the pooled t-test for the comparison with the placebo group.

‖The worst-case analysis assumed the 3.9 percent rate of progression of stenosis found in the placebo group, at constant variance, for each of the patients who withdrew from the study (four in the placebo group, five in the simvastatin–niacin group, three in the antioxidant-therapy group, and two in the group that received simvastatin–niacin plus antioxidants). A total of 160 patients are included in this analysis.

**Unadjusted P<0.02 by the pooled t-test for the comparison with the placebo group.

††Unadjusted P≤0.05 by the pooled t-test for the comparison with the placebo group.

brinogen (r=0.19, P=0.03); and diastolic blood pressure (r=0.16, P=0.06).

Frequency of Clinical Cardiovascular Events

The composite primary end point included death from coronary causes, confirmed myocardial infarction or stroke, or revascularization for worsening ischemic symptoms. Two secondary composite end points are also examined in Table 4. Vital status was ascertained at 38 months for all 160 patients enrolled; follow-up information for 159 patients was complete, including records of events from the patients' physicians. Events were classified with the use of preestablished criteria by a consensus panel that was blinded to the treatment-group assignment. Kaplan–Meier curves for the four treatment groups are provided in Figures 2A and 2B. The risk of the composite primary end point was 90 percent lower in the simvastatin–niacin group than in the placebo group (P=0.03). The risk in the other treatment groups did not differ significantly from that in the placebo group. Kaplan–Meier curves for all patients who were given simvastatin plus niacin and those who were not, and for all patients who were given antioxidant vitamins and those who were not are shown in Figures 2C and 2D. These factorial analyses — part of the original study design — demonstrated a 60 percent reduction in risk with simvastatin–niacin (P=0.02) and a small, nonsignificant increase in risk with antioxidants. Because of the tendency toward an interaction between the two active therapies with adverse effects on clinical end points (P=0.13), these factorial comparisons tend to reflect a conservative underestimate of the clinical benefit from either therapy alone, which these data suggest is substantial for simvastatin plus niacin and small, at best, for antioxidant vitamins.

DISCUSSION

When patients with coronary disease, normal LDL cholesterol levels, and low HDL cholesterol levels were treated for three years with simvastatin plus niacin, proximal coronary stenosis regressed slightly, on average, and the rate of major clinical events was 90 percent lower than that in the placebo group. Conversely, despite increased plasma vitamin levels and resistance of LDL to oxidation, we found no significant benefits from this relatively high-dose regimen of four antioxidant agents. There was only a trend (P=0.16 for the comparison with placebo) toward a slowing of the progression of stenosis, and there was minimal reduction in the rate of clinical events. Contrary to the hypothesis that antioxidants might provide the greatest benefit in early lesions, they had no effect on stenoses of 0 to 29 percent of the luminal diameter (Table 3).

TABLE 4. NUMBERS OF PATIENTS WITH AT LEAST ONE EVENT AMONG VARIOUS CATEGORIES OF MAJOR CLINICAL EVENTS DURING THE 38-MONTH FOLLOW-UP PERIOD.*

CARDIOVASCULAR EVENT	PLACEBOS (N=38)	SIMVASTATIN–NIACIN (N=38)	ANTIOXIDANT VITAMINS (N=42)	SIMVASTATIN–NIACIN PLUS ANTIOXIDANTS (N=42)
		number		
Death				
Noncardiovascular causes	0	0	0	0
Cardiovascular causes	1	0	0	1
Nonfatal infarction				
Myocardial	4	1	1	3
Cerebral	2	0	2	0
Composite of death from cardiovascular causes or nonfatal infarction	7	1	3	3
Revascularization procedure				
Coronary bypass surgery	2	0	3	3
Coronary angioplasty or stenting	4	1	5	2
Carotid endarterectomy	0	0	0	0
Peripheral endarterectomy or grafting	0	0	2	0
Composite of death from cardiovascular causes, nonfatal infarction, or revascularization procedure†	9	1‡	9	6
Hospitalization for confirmed ischemia without revascularization	3	0	4	1
Composite of death from cardiovascular causes, nonfatal infarction, revascularization procedure, or hospitalization for confirmed ischemia	12	1§	11	6

*All enrolled patients were included in this intention-to-treat analysis.

†This composite was the primary clinical end point.

‡P=0.04 by Fisher's exact test for the comparison with the placebo group (adjusted for multiple comparisons).

§P=0.003 by Fisher's exact test for the comparison with the placebo group (adjusted for multiple comparisons).

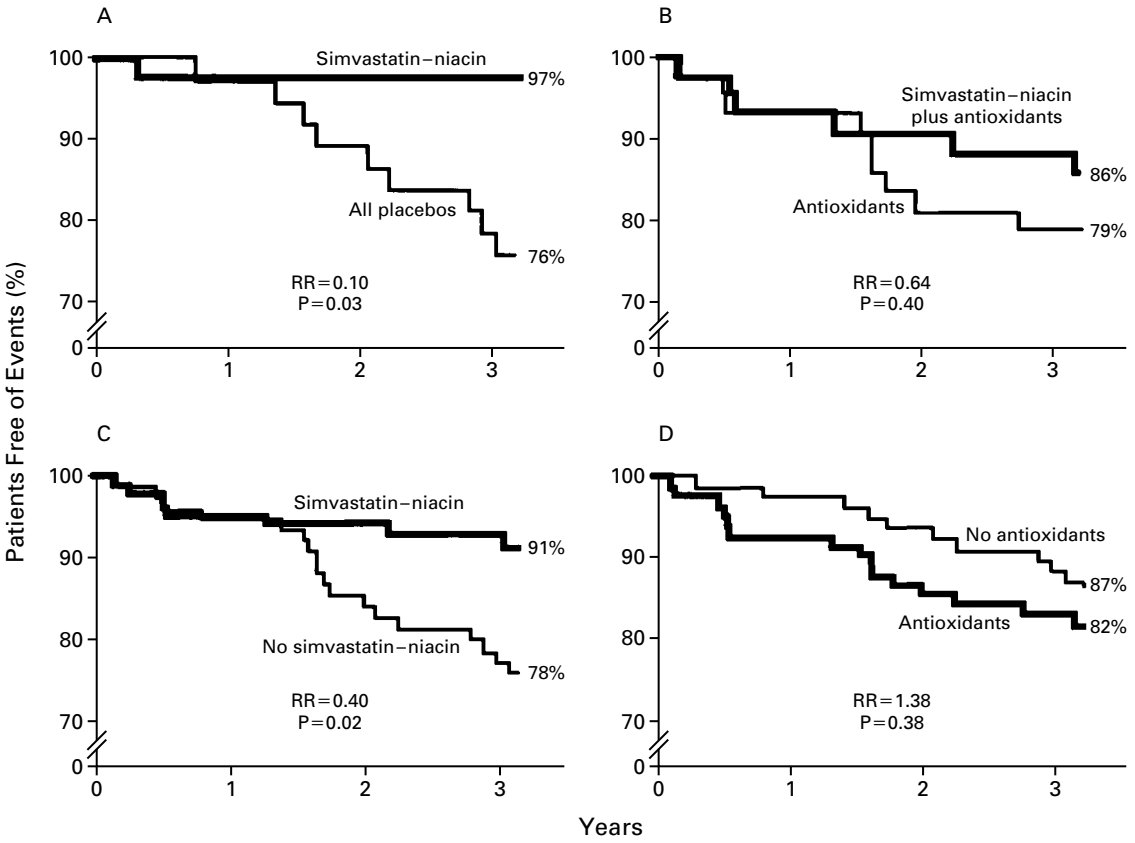

Figure 2. Kaplan–Meier Curves for the Time to the First of the Components of the Composite Primary Clinical End Point (Death from Coronary Causes, Nonfatal Myocardial Infarction, Confirmed Stroke, or Revascularization for Worsening Ischemia).

Panel A shows the curves for the 38 patients in the simvastatin–niacin group and for the 38 in the placebo group; the relative risk (RR) of an event was 0.10 (95 percent confidence interval, 0.01 to 0.81). Panel B shows the curves for the 42 patients assigned to receive simvastatin–niacin and antioxidants and for the 42 in the antioxidant group. Panel C shows the curves for all 80 patients who were assigned to receive simvastatin plus niacin and for the 80 who were not. Panel D shows the curves for the 84 patients who were assigned to receive antioxidants and for the 76 who were not.

These findings concur with the results of four large negative trials of vitamins.[29-32]

The clinical and angiographically measurable benefits of simvastatin plus niacin were greater than those that would be expected from statins alone. We found regression of stenosis, rather than slowed progression,[3] and a reduction of 60 to 90 percent, instead of 24 to 34 percent, in the rate of events.[3,4] These results were not entirely unexpected. They are consistent with the epidemiologic projection of a 1 percent reduction in cardiovascular risk for each 1 percent increase in the HDL cholesterol level and, independently, a 1 percent reduction in risk for each 1 percent decrease in the LDL cholesterol level.[1] For this study, the approximate risk reduction, by this simplified estimate, would be 68 percent (corresponding to a 26 percent increase in the HDL cholesterol level plus a 42 percent decrease in the LDL cholesterol level). Similarly, in another trial, the risk of the same composite end point was reduced by 80 percent with the use of niacin plus colestipol, which led to a 43 percent increase in the HDL cholesterol level and a 32 percent decrease in the LDL cholesterol level.[7] The greater-than-expected clinical and angiographically measurable benefits of simvastatin plus niacin may, in part, be due to a proposed[33] dual therapeutic pathway: statins principally reduce the number of LDL particles; niacin principally increases HDL2 levels and the buoyancy of LDL particles by diminishing hepatic lipase activity,[33] one determinant of low HDL2 levels.[34,35]

Surprisingly, when antioxidants were combined with simvastatin and niacin, arterial and clinical benefits tended to diminish as compared with those achieved with simvastatin and niacin alone. The adverse interaction between these two therapeutic strategies was significant ($P=0.02$) in terms of the angiographic end

points but not significant (P=0.13) in terms of the clinical end points. This interaction appears to result from substantial and specific blunting by these vitamins of the expected increase in the level of the protective HDL2 subfraction[26] — an effect that has been found with the potent nonvitamin antioxidant probucol.[28]

A limitation due to the small size of this study is the relatively wide confidence intervals for the apparently substantial clinical effects of combined antihyperlipidemic therapy. The credibility of the clinical results gains support from the parallel and compelling effects on the progression of stenosis.

These findings apply to the roughly 40 percent of patients with coronary disease who have low HDL cholesterol levels but who rarely use combination therapy targeted at both LDL cholesterol and HDL cholesterol and who frequently use antioxidant vitamins because of unsupported perceptions. The observed reduction of 60 to 90 percent in the rate of major coronary events with combination simvastatin–niacin therapy, if confirmed, would represent a substantial advance over current practice.

It is important to distinguish these results and those of other trials of antioxidants[29-32] from the prevailing view that the oxidation of LDL contributes in an important, although not a unique,[36] way to atherogenesis. Eventually, more potent, more appropriately targeted, or less HDL2-adverse antioxidants may prove effective. Unless more compelling evidence appears,[37] we see little justification for the use of antioxidant vitamins for the prevention of cardiovascular events, particularly since they lower the HDL2 level and interfere with the HDL2-raising effects of concomitant lipid-altering therapy.

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