Factors Influencing the Formation of New Human Coronary Lesions: Age, Blood Pressure, and Blood Cholesterol

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ABSTRACT

Background. The Cholesterol Lowering Atherosclerosis Study, a controlled angiographic trial, has reported that new native coronary artery lesions are significantly reduced by aggressive blood lipid lowering therapy with colestipol plus niacin. To study factors relevant to primary atherosclerosis prevention, we have conducted an epidemiologic analysis of new native coronary lesion formation in placebo-treated patients.

Methods. Univariate and multivariate logistic regression procedures were used to examine age at entry into the study, number of years since bypass, body weight, diastolic and systolic blood pressure, plasma total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, non-HDL-cholesterol, and apolipoproteins A-I,B, and C-III.

Results. Significant univariate protective factors were older age ($P<.006$), reduction of total plasma cholesterol ($P<.040$), and systolic ($P<.024$) and diastolic ($P<.022$) blood pressure. Significant multivariate protective factors were older age ($P<.005$) and reduction in systolic blood pressure ($P<.021$). Blood pressure effects were not associated with use of specific antihypertensive agents.

Conclusions. These data provide additional support for the control of hypertension and reduction of blood cholesterol level for primary and secondary ischemic heart disease prevention. They also indicate the existence of a population at high risk for early coronary lesion formation and the need for improved means to identify such individuals prior to the onset of clinical manifestations of ischemic heart disease. (*Am J Public Health.* 1991;81:1180–1184.)

Introduction

CLAS (Cholesterol Lowering Atherosclerosis Study) was a randomized, placebo-controlled angiographic trial testing the hypothesis that blood lipid lowering with colestipol plus niacin would slow or reverse the atherosclerotic process. CLAS was a secondary prevention trial involving men, ages 40 to 59 years, who had had previous aortocoronary bypass surgery. CLAS angiograms were evaluated for vessel closure, changes in degree of stenosis, and formation of new lesions. We have previously reported significant treatment benefits in overall coronary status of both native vessels and bypass grafts, including reduction of formation of new lesions.[1] Following publication of CLAS results, angiographic trials testing nifedipine[2] and dipyridamole plus aspirin[3] have also reported reduced formation of new coronary lesions, which suggests that pathways early in atherogenesis may be beneficially modified by several different types of therapy. Studies of atherogenesis in animal models and cultured cell systems suggest a variety of ways in which factors initiating lesion formation might differ from those that cause progression of established lesions. The relationship of risk factors to prevalence of human coronary lesions[4] and change in established coronary lesions[5–20] has been extensively studied by angiography, but there are no risk analyses for new coronary lesion formation. To explore risk factor effects on human new coronary lesion formation we conducted an analysis of risk for disease with nondisease in placebo-treated CLAS subjects by comparing subjects who developed new coronary lesions with those who did not. The influence of diet on new lesion formation has been reported previously.[21] We now address the association of clinical variables with the development of new lesions.

Methods

Study Population

Subjects were nonsmoking males, ages 40 to 59 years, with progressive symptomatic atherosclerosis who had had previous coronary bypass surgery. Screening procedures, criteria for exclusion, standard visit protocols, and basic intervention goals were reported earlier.[22] One hundred eighty-eight subjects were randomized into two treatment groups of 94 each; 162 completed the study, 82 of whom were placebo-treated. Average age at entry of all placebo subjects was 54.5 ± 0.5 (SEM) and average blood pressure was 123 mm Hg ± 1.5 (SEM)/80 ± 1.0 (SEM). Thirty percent never smoked and 70% had quit smoking more than 6 months before trial entry. Twenty-four-hour urine specimens were examined for nicotine and cotinine every 6 months to monitor nonsmoking status. Dietary goals for the placebo group were as follows: total fat calories to provide 26% of energy, less than 5% of energy from saturated fatty acids, 10% of energy from polyunsaturated fatty acids, and less than 250 mg cholesterol per day. One-on-one diet counseling was conducted at each clinic

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visit with a review of fat and cholesterol intake in computerized 7-day food records from the preceding week. Levels of physical activity were moderate as judged from questionnaires and estimates of energy expenditure from records of caloric intake for the 7 days preceding each clinic visit.

Data Collection

Angiographic. Baseline coronary angiography was performed immediately before randomization. A repeat angiogram was performed at 2 years by the same angiographer, who was blinded to the treatment assignment. Coronary angiogram evaluation procedures have been described in detail previously.[1,22] All lesions greater than 20% diameter stenosis were identified. Film pairs showing identical coronary artery views were mounted side by side on two Vanguard projectors and viewed simultaneously by two expert angiographers who did not know the subject's demographic and clinical characteristics, treatment assignment, or temporal order of the angiograms. The angiographers were not shown ventriculograms and other angiograms. Working independently, the two angiographers identified all visible lesions in one film (assigned at random), recorded this information, and then shared it to reach a consensus. In this manner a total of 1831 lesions were recognized and evaluated, 82% of which were identified independently by both panelists. For the 1501 lesions identified independently by both panelists, agreement within ±10% stenosis occurred in 76%. After reaching a consensus on the first film, panelists examined the second film alongside the first and compared all lesions first separately and then together. After all film pairs were evaluated, the code for film order was broken and lesions recorded in a later angiogram, but not in a first, were tabulated.

Body Weight, Blood Pressure, Plasma Lipids, and Medication History. Body weight, blood pressure, and plasma lipids were measured at every visit.[22] Blood lipids and lipoprotein cholesterol levels were determined by Lipid Research Clinics methodology standardized against reference materials supplied by the Centers for Disease Control.[23] LDL-cholesterol levels were calculated with the equation of Friedewald et al.[24] Baseline levels were the means of the first three screening visits. Postrandomization visits were scheduled every month for the first 6 months and bimonthly thereafter. On-trial values were the average of all postrandomization visits weighted by the scheduled interval between treatment visits. Apolipoprotein determinations were performed by the Oklahoma Foundation for Medical Research.[22] All medications, including over-the-counter drugs, were recorded at semiannual visits (0, 6, 12, 18, and 24 months after randomization).

At study entry 36% of the 82 CLAS placebo subjects reported use of antihypertensive medications and 93% of this group remained on these agents during the trial. The most common drugs and dosage were propranolol 40 mg/day (33% of subjects), hydrochlorothiazide 50 mg/day (13%), and dyazide 50 mg/day (10%). Eight percent of CLAS placebo subjects reported one or more on-trial uses of either nifedipine, diltiazem, or verapamil. Eighty percent of subjects took either aspirin, Ascriptin, or acetaminophen on one or more occasions during the trial.

Statistical Analyses. Univariate logistic regression procedures were used to determine which independent variables were predictive of the development of new lesions. Potentially predictive independent variables included age at entry into the study, number of years since bypass, body weight, diastolic and systolic blood pressure, plasma total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, non-HDL-cholesterol, and apolipoproteins A-I, B, and C-III. Age and years since bypass were analyzed by values at baseline. All other variables were analyzed by values at baseline, as well as mean on-trial, to explore the temporal relationship of these variables to lesion formation. In addition, the difference (baseline minus mean on-trial) was analyzed to assess the relationship between change in these variables and new lesion formation. We chose to compare baseline to mean on-trial values of each independent variable for two reasons. First, given the relatively small sample size of this study and the fact that each subject contributed a potential of 15 on-trial data points for each variable, it was not feasible to assess the significance of each variable at each time point. Second, given the short time period of this study (2 years) relative to the several decades of life, over which atherosclerotic disease develops, we felt that assessing the association of overall on-trial changes relative to prerandomization measures provided a more meaningful analysis. For each independent variable, univariate odds ratios (OR) and associated 95% confidence intervals (CI) were computed[25]; all P values for trends in relative risk are based on two-tailed tests. Stepwise logistic regression was used as a final step to arrive at a multivariate model of statistically independent predictors of new lesion formation.

Results

Of the 82 subjects in the placebo group, 18 had developed new lesions in the 2-year period between angiograms, as previously reported.[1] Thirteen among the 18 subjects with new lesions had a single new lesion, 3 had two new lesions, and 1 each had three and four new lesions. Among the 26 new lesions, 15 were in ungrafted patent arteries, 1 was proximal to complete occlusion in an ungrafted artery, 6 were proximal to open grafts, 2 were distal to open grafts, and 2 were distal to closed grafts. Nine of the new lesions were between 20% and 29% diameter stenosis and 6 were between 30% and 39%. Two lesions were 40% diameter stenosis, 4 were 50%, and 1 each were 60%, 70%, 75%, 80%, and 90% stenosis.

With subjects classified by presence or absence of new lesions, mean values of major clinical variables are presented in Table 1. Descriptively, compared to subjects who did not develop new lesions, subjects who developed new native lesions were usually younger at study entry, had recently undergone bypass surgery, had lost less weight on-trial, and had increased both systolic and diastolic blood pressure while on-trial. Those who developed new lesions also showed minor changes in total cholesterol and LDL-cholesterol (less than 1% decrease in both), a 2% decrease in non-HDL-cholesterol, a 5% increase in HDL-cholesterol, and a 10% decrease in triglycerides. In comparison, CLAS placebo subjects who did not develop new lesions demonstrated larger decreases in total, LDL, and non-HDL-cholesterol (6%, 7%, and 7%, respectively), no change in HDL-cholesterol, and an 8% decrease in triglycerides. Subjects developing new native lesions also had a lower average baseline value of apolipoprotein B (average 111.1 mg/dL compared to 124.1 mg/dL in subjects not developing new lesions) and demonstrated an 8% increase in this variable while on-trial. Subjects who did not develop new lesions showed no average on-trial change in apolipoprotein B. Table 1 also presents the univariate ORs and 95% CIs for each variable. All variables have been divided by their sample standard deviation (SD) so that the resulting ORs represent the relative risk for a 1 SD increase in that variable.

TABLE 1—Independent Variable Means by Lesion Group

Variables	New Lesions Mean ± SD (n = 18)	No New Lesions Mean ± SD (n = 64)	SD[a]	OR[b]	95% CI
Age at study entry	51.7 ± 5.0	55.2 ± 15.7	4.4	0.5	0.3–0.8
Years since bypass	2.4 ± 1.5	2.9 ± 2.3	2.3	0.7	0.4–1.3
Body weight (lbs)					
Baseline	178.3 ± 16.7	177.7 ± 23.3	21.9	1.0	0.6–1.7
On-trial	178.1 ± 16.3	176.8 ± 25.2	23.4	1.1	0.6–1.8
Difference	0.2 ± 6.1	0.9 ± 5.8	5.9	0.9	0.5–1.5
Diastolic BP (mm Hg)					
Baseline	80.8 ± 9.3	80.3 ± 8.3	8.5	1.1	0.6–1.8
On-trial	83.4 ± 7.3	80.1 ± 7.1	7.3	1.6	0.9–2.9
Difference	−2.6 ± 4.5	0.2 ± 4.2	4.4	0.5	0.3–0.9
Systolic BP (mm Hg)					
Baseline	118.8 ± 11.2	124.7 ± 12.0	12.0	0.6	0.3–1.1
On-trial	121.4 ± 10.2	123.0 ± 11.5	11.2	0.9	0.5–1.5
Difference	−2.7 ± 7.1	1.6 ± 6.3	6.9	0.5	0.3–0.9
Plasma total cholesterol (mmol/L)					
Baseline	6.3 ± 1.0	6.3 ± 0.9	0.9	1.0	0.6–1.6
On-trial	6.2 ± 1.2	5.0 ± 0.8	0.9	1.3	0.8–2.1
Difference	0.1 ± 0.5	0.3 ± 0.5	0.5	0.5	0.3–1.0
LDL-cholesterol (mmol/L)					
Baseline	4.3 ± 0.8	4.4 ± 0.8	0.8	0.9	0.5–1.5
On-trial	4.2 ± 1.0	4.1 ± 0.7	0.8	1.2	0.7–2.1
Difference	0.0 ± 0.5	0.3 ± 0.5	0.5	0.6	0.3–1.0
HDL-cholesterol (mmol/L)					
Baseline	1.1 ± 0.2	1.1 ± 0.3	0.2	0.8	0.5–1.3
On-trial	1.1 ± 0.2	1.1 ± 0.2	0.2	1.0	0.6–1.6
Difference	−0.1 ± 0.1	0.0 ± 0.1	0.1	0.7	0.5–1.1
Non-HDL-cholesterol (mmol/L)					
Baseline	5.2 ± 1.0	5.1 ± 0.9	0.9	1.0	0.6–1.7
On-trial	5.1 ± 1.3	4.8 ± 0.8	0.9	1.3	0.8–2.1
Difference	0.1 ± 0.5	0.3 ± 0.5	0.5	0.6	0.3–1.0
Triglycerides (mmol/L)					
Baseline	2.0 ± 1.0	1.7 ± 1.0	1.0	1.3	0.8–2.1
On-trial	1.8 ± 0.9	1.5 ± 0.9	0.9	1.3	0.8–2.1
Difference	0.2 ± 0.3	0.1 ± 0.4	0.4	1.1	0.7–1.9
Apo-A-I (mg/dL)					
Baseline	114.9 ± 15.4	115.6 ± 19.0	18.2	1.0	0.6–1.6
On-trial	123.8 ± 11.6	121.9 ± 15.4	15.7	1.1	0.7–1.9
Difference	−8.9 ± 14.9	−6.3 ± 15.8	15.6	0.9	0.5–1.4
Apo-B (mg/dL)					
Baseline	111.1 ± 25.7	124.1 ± 26.7	26.9	0.6	0.3–1.0
On-trial	119.8 ± 24.2	124.1 ± 22.2	22.6	0.8	0.5–1.4
Difference	−8.8 ± 21.1	0.0 ± 21.0	21.2	0.6	0.4–1.1
Apo-C-III (mg/dL)					
Baseline	5.6 ± 2.8	4.6 ± 2.1	2.3	1.5	0.9–2.5
On-trial	5.7 ± 3.2	4.7 ± 2.5	2.6	1.4	0.8–2.2
Difference	0.0 ± 1.7	−0.1 ± 1.4	1.4	1.1	0.6–1.8

Note. Difference = baseline minus mean ontrial value; CI = confidence interval.
[a]SD = Standard deviation for entire sample (N = 82).
[b]Odds ratio = relative risk per SD change of independent variable (relative to no change).

Independent variables showing univariately significant trends in relative risk for new lesion formation are displayed in more detail in Table 2. To show the trend in relative risk, each variable was categorized into four levels using the sample quartiles, and ORs were estimated for each level relative to the first quartile.

Age at entry into the study was protective for new lesions; thus, older men were less likely to develop new lesions. Dividing the total group of 82 men at the median age (54.5 years), the risk of new lesion development for men above the median was 0.2 times that of men below or at the median age (95% CI = 0.1–0.7). Conversely, the risk for new lesion formation in men younger than 55 years at study entry was 4.8 times that of older men. Inclusion of other significant independent clinical and diet variables[21] did not alter the significance of the influence of age on lesion development.

Changes in both diastolic and systolic blood pressure and total plasma cholesterol from baseline to mean on-trial values were also significant univariate predictors of new lesions (Table 2). Decreases in blood pressure and total plasma cholesterol from baseline to on-trial conferred lower risk for development of new atherosclerotic lesions. Other independent variates, including HDL-, LDL-, and non-HDL-cholesterols, apolipoproteins A-I, B, and C-III, triglycerides, body weight, and years since bypass, were not significantly associated with new lesion formation. Finally, variables indicating whether or not a subject had used platelet-active medications, calcium channel blockers, or other antihypertensive medications were not significantly related to new lesion formation.

To investigate the differential effects of lipids by age, interactions between a dichotomized age variable (dichotomized at the median age at study entry) and plasma lipids measured at baseline and on-trial were included in the logistic regression procedure. Two significant interactions emerged in these analyses. The first interaction was an age-on-trial HDL-cholesterol interaction ($\chi^2 = 3.96$; df = 1; $P = .046$), with the parameter estimate indicating a protective effect for HDL-cholesterol confined to subjects older than 55 years. The interaction between age and on-trial triglycerides was also significant ($\chi^2 = 7.00$; df = 1; $P = .01$) with an increased risk for lesion development due to increased triglyceride level occurring in the older age group. In both cases, the main effect of age remained significant after inclusion of these interactions.

To determine which of the univariately significant variables were independently predictive of new native lesions, a stepwise logistic regression analysis was performed (Table 3). Age at study entry was the first independent variable to enter the model; the risk for development of new native lesions was decreased by a factor of 0.4 for every 4.4 years (ISD) of age. After adjusting for age, the change in systolic blood pressure from baseline to on-trial was also significantly predictive of new lesion formation; each 7 mm Hg decrease in systolic blood pressure was as-

sociated with the risk of new lesions being decreased by a factor of 0.5. No other variables were significantly related to lesion development after inclusion of these two variables.

Of the 18 subjects who had developed new lesions, 11 had new lesions in native arteries with related grafts, while 7 had new lesions in native arteries without a related graft. These two subgroups were separately compared to the 64 subjects who did not develop new lesions. Parameter estimates for the final model (age at entry into study and change in systolic blood pressure) did not change from those displayed in Table 3, suggesting that these effects are the same in native arteries with and without related bypass grafts.

Discussion

Our analyses are focused on the appearance of new lesions visible by angiography because these indicate an increase in the extent of raised intrusions into the coronary lumen, the most significant single anatomic predictor of ischemic heart disease (IHD) at autopsy.[26] We are concerned primarily with relationships within the placebo group because new lesions were more common here and because these relationships are more relevant to primary IHD prevention than those among drug-treated subjects. Reduction of new lesions in secondary prevention has merit, but reduction of new lesions in primary prevention could benefit many more individuals and might lead to population-wide control of IHD. We have previously reported reduction of new lesions in secondary prevention in CLAS through aggressive treatment with colestipol plus niacin.[1] This treatment reduced average total plasma cholesterol from 6.36 to 4.65 mmol/L and reduced the relative risk of new lesions by a factor of 0.4 ($P = .03$). We have also reported an analysis of diet records of CLAS placebo subjects relevant to primary prevention that indicated that reduction of new lesions might be accomplished by reducing dietary fat.[21] We now report an additional analysis of risk factors relevant to primary prevention that have significant effects on new lesion formation independent of diet. In CLAS placebo subjects, risk for new lesions was predicted by age, on-trial reduction of total plasma cholesterol, and on-trial reduction of both systolic and diastolic blood pressure. When these four univariate predictors competed in stepwise logistic regression, age and change in systolic blood pressure were found to be significant. The effect of age is significant in analyses that pool drug subjects with placebo.

TABLE 2—Univariately Significant Predictors of New Lesion Formation[a]

	OR	95% CI	*P* trend
Age at entry to study, y			
40 to 52	1.0		.006
>52 to 54.5	0.3	(0.1, 1.1)	
>54.5 to 58	0.1	(0.02,0.6)	
>58	0.1	(0.03,0.8)	
Change in total blood cholesterol (mmol/L)			
≤0	1.0		.040
>0 to 0.2	0.8	(0.2, 2.9)	
>0.2 to 0.6	0.6	(0.2, 2.5)	
>0.6	0.2	(0.1, 1.4)	
Change in diastolic blood pressure (mmHg)			
≤−4	1.0		.022
>−4 to −1	0.4	(0.1, 1.5)	
>−1 to 3	0.3	(0.1, 1.5)	
>3	0.2	(0.04,1.1)	
Change in systolic blood pressure (mmHg)			
≤−3	1.0		.024
>−3 to 1	0.6	(0.2, 2.3)	
>1 to 5	0.4	(0.1, 1.8)	
>5	0.2	(0.04,1.3)	

Note. OR = odds ratio; CI = confidence interval.
[a]Change variables = baseline minus mean on-trial.

TABLE 3—Stepwise Logistic Regression

Variable	OR[a]	95% CI[b]	*P*
Age at study entry	0.4	0.2–0.8	.005
Change in systolic blood pressure	0.5	0.3–0.9	.021

[a]Odds ratio interpreted as change in risk per standard deviation of age or standard deviation change in systolic blood pressure.
[b]CI = confidence interval.

The multivariate stepwise model associated with on-trial change in systolic blood pressure and age indicates that reduction of systolic blood pressure by 10 mm Hg reduced the risk of the new lesion development by 60% in men of median age 54.5 years. It is important to note that the principal antihypertensive agents used in CLAS placebo subjects were propranolol, hydrochlorothiazide, and dyazide, not slow calcium channel antagonists. When variables indicating whether or not a subject had taken calcium channel blockers or other antihypertensive medications were introduced into logistic regression, they were not significantly related to new lesion formation. We conclude that reduction of blood pressure level per se, rather than the agent used to produce the reduction, was the significant influence in CLAS placebo subjects. Thus, modest changes in blood pressure perceptibly altered atherogenesis at the stage of raised lesion development. This finding is compatible with the large body of epidemiologic evidence for long-term effects of blood pressure on population IHD rates.[27,28] Trials of antihypertensive therapy such as the Multiple Risk Factor Intervention Trial[29] may have failed to show reduced IHD rates because benefits from reduced new lesion formation were masked by catastrophic events in existing coronary lesions.

In summary, placebo group data from CLAS indicate that formation of new intrusive coronary lesions is significantly

influenced by age and change in blood cholesterol and blood pressure level. The effects of blood pressure and blood cholesterol are compatible with findings from IHD epidemiology and confirm that it is appropriate to reduce these risk factors for primary IHD prevention. Age was observed to have a negative effect, with more young subjects showing new lesion formation. This indicates the need for improved methods to identify young individuals who form new coronary lesions at accelerated rates. □

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