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Improved Stenosis Geometry by Quantitative Coronary Arteriography After Vigorous Risk Factor Modification

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This study is a randomized, controlled, blinded, arteriographic trial to determine the effects of a low-cholesterol, low-fat, vegetarian diet, stress management and moderate aerobic exercise on geometric dimensions, shape and fluid dynamic characteristics of coronary artery stenoses in humans. Complex changes of different primary stenosis dimensions in opposite directions or to different degrees cause stenosis shape change with profound effects on fluid dynamic severity, not accounted for by simple percent narrowing. Accordingly, all stenosis dimensions were analyzed, including proximal, minimal, distal diameter, integrated length, exit angles and exit effects, determining stenosis shape and a single integrated measure of stenosis severity, stenosis flow reserve reflecting functional severity. In the control group, complex shape change and a stenosis — molding characteristic of statistically significant progressing severity occurred with worsening of stenosis flow reserve. In the treated group, complex shape change and stenosis molding characteristic of significant regressing severity was observed with improved stenosis flow reserve, thereby documenting the multidimensional characteristics of regressing coronary artery disease in humans.

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The Lifestyle Heart Trial[1] is a randomized, controlled, blinded, arteriographic trial to test the hypothesis that (1) vigorous modification of risk factors stops progression or causes regression of coronary artery stenosis, and (2) stenosis shape changes or undergoes remolding with progression or regression of coronary atherosclerosis in humans to the extent that no single dimension reflects the essential changes observed.

The initial report of this trial[1] describes the experimental design, risk factor intervention and changes in percent diameter stenosis because percent diameter stenosis is the most widely used measure of stenosis severity. However, percent stenosis is an incomplete measure of stenosis severity because length, absolute lumen area and shape effects are not accounted for and correlate poorly with the functional measure of coronary artery stenoses, coronary flow reserve.[2–10] The cumulative effects of multidimensional geometric changes on fluid dynamic characteristics of stenoses suggest that simple concepts of progression/regression need to be redefined in terms of shape changes or remolding of stenoses. Therefore, to definitively address whether progression or regression occurs in humans with risk factor modification, we performed multidimensional analysis of arteriographic stenoses to determine stenosis flow reserve as a single functional measure of severity incorporating all geometric dimensions of each stenosis.

Background: Seven previous coronary arteriographic trials of cholesterol lowering by diet and drugs have been reported.[11–17] Kuo et al[11] and the Leiden Intervention Trial[12] suggested that progression of stenoses was prevented by a cholesterol-lowering diet and drugs but these studies lacked untreated control subjects. Nash[13] and Nikkila[14] and their co-workers showed prevention of progression by cholesterol-lowering drugs compared with untreated control subjects who were not randomized. In a randomized controlled trial of clofibrate, Cohn et al[15] showed equal progression of disease in 63 and 69% of treated and control groups without regression.

The National Heart, Lung, and Blood Institute Type II Coronary Intervention Study[16] was a randomized, controlled trial of diet and cholestyramine showing less arteriographic progression (32%) in the treated

group compared with a progression of 49% in the control group, a significant difference. However, no regression was observed, and 32% of the treated group still showed progression of disease. The Cholesterol Lowering Atherosclerosis Study trial[17] was a randomized controlled arteriographic trial of diet, colestipol and niacin showing regression in 16% of treated patients compared with 2% regression in control groups. Appearance of new lesions was prevented and global severity scores were significantly less in the treated group compared with control subjects. However, in the treated group 39% still showed progression of disease. Ornish et al[1] demonstrated cessation of progression or regression of coronary artery stenoses in a large proportion of subjects on a strict low-fat vegetarian diet but not in control subjects on a standard American Heart Association diet.[1] Brown et al[18] demonstrated significant regression in subjects with familial hypercholesterolemia treated by double drug therapy for reducing serum cholesterol.

METHODS

Automated quantitative arteriographic analysis was used in this study because (1) complex shape changes of stenosis are accounted for with incorporation of all dimensions of length, percent narrowing, absolute lumen area and shape effects; (2) visual interpretations of arteriograms are marked by such great interobserver and intraobserver variation that comparisons of arteriograms from different subjects or the same subject at different times have limited quantitative accuracy for assessing severity or changes in severity of stenoses[2-10]; (3) the reproducibility of automated quantitative coronary arteriographic analysis of primary dimensions in vivo is ± 3 to ± 5% in absolute dimensions, with a precision in phantoms of ± 0.1 mm[2,4-7,19-21] so that small changes in stenosis geometry could be reliably measured in control and treated groups; and (4) no previous study has used automated quantitative coronary arteriography or measured all stenosis dimensions in order to define the total geometric changes occurring with regression or progression.

Study patients: Patients were men or women, 35 to 70 years old, who had documented coronary artery disease by arteriography, had no recent myocardial infarction or were not taking lipid-lowering drugs, had left ventricular ejection fraction >25%, and resided in the San Francisco area to participate in the risk modification program. After all groups gave informed consent and were randomized initial and follow-up, coronary arteriography was performed using the standard percutaneous femoral approach as previously described.[1,2]

Modification of risk factors was achieved by the Preventive Medicine Research Institute in San Francisco as previously described[1] and summarized here. It consisted of a low-cholesterol (<5 mg/day), low-fat (<10% of calories) vegetarian diet with 15% protein and 75% complex carbohydrate augmented with vitamin B-12. Patients stopped smoking, practiced stress management, and participated in moderate aerobic exercise on a daily basis.

Quantitative coronary arteriography: The cardiac catheterization laboratories in San Francisco were calibrated for quantitative arteriographic analysis by the University of Texas staff. Meticulous records of the view angles, x-ray exposures, image intensifier, x-ray tube, patient distances and reference catheter dimensions were maintained. Follow-up arteriograms used these same characteristics in order to reproduce views and exposures as closely as possible on follow-up studies.

Initial and follow-up arteriograms were analyzed simultaneously in pairs by a technician unaware of clinical data or group assignment using automated border recognition and stenosis analysis techniques in order to avoid the potential bias, imprecision and uncertainties of visual interpretation. Cine arteriographic frames of orthogonal views were digitized on a Spatial Data System, Eyecom II online with a VAX 11/780 for each stenosis involving a major artery. Absolute and relative stenosis dimensions were measured with a computer program providing automatic detection of vessel borders (Figure 1). The theory and equations for predicting stenosis flow reserve from these dimensions have previously been described.[2,5-7,19-21]

The primary stenosis dimensions measured by the automated arteriographic program include proximal diameter and cross-sectional lumen area, minimal diameter and area, distal diameter and area, the exit angle, exit shape effects, and calculated measures of severity including percent diameter stenosis, percent area narrowing, integrated length-area effects and stenosis flow reserve.

Stenosis flow reserve is a measure of severity integrating all these dimensions into a single number reflecting the capacity for increasing flow through the observed geometry for a standardized aortic pressure. It is based on the concept of coronary flow reserve proposed 17 years ago by Gould et al[2,3] that has evolved into an accepted measure of functional stenosis severity.[2-10,19-21] Our arteriographic analysis has been validated in 3 separate experimental studies,[4,7,21] applied in humans[2,19] and used routinely in approximately 4,000 clinical arteriograms.

Figure 1 illustrates the pressure flow relation for a stenosis based on all its arteriographic dimensions, shown by the downward curving. Stenosis flow reserve is defined as the intersection of the downward curved line characterizing stenosis severity by stenosis geometry with the experimentally determined upward straight line characterizing maximal flow for given pressure in a maximally vasodilated coronary artery bed.[2,7] Flow is expressed as a relative multiple of rest flow, Q/Qrest under standardized hemodynamic conditions of 100 mm Hg aortic pressure, and standardized normal maximal flow reserve of 5 times baseline. Compared with direct measurements by electromagnetic flow meter in experimental animals, there is a close correlation between arteriographic stenosis flow reserve based on arteriographic dimensions and directly measured coronary flow reserve by flow meter for comparable hemodynam-

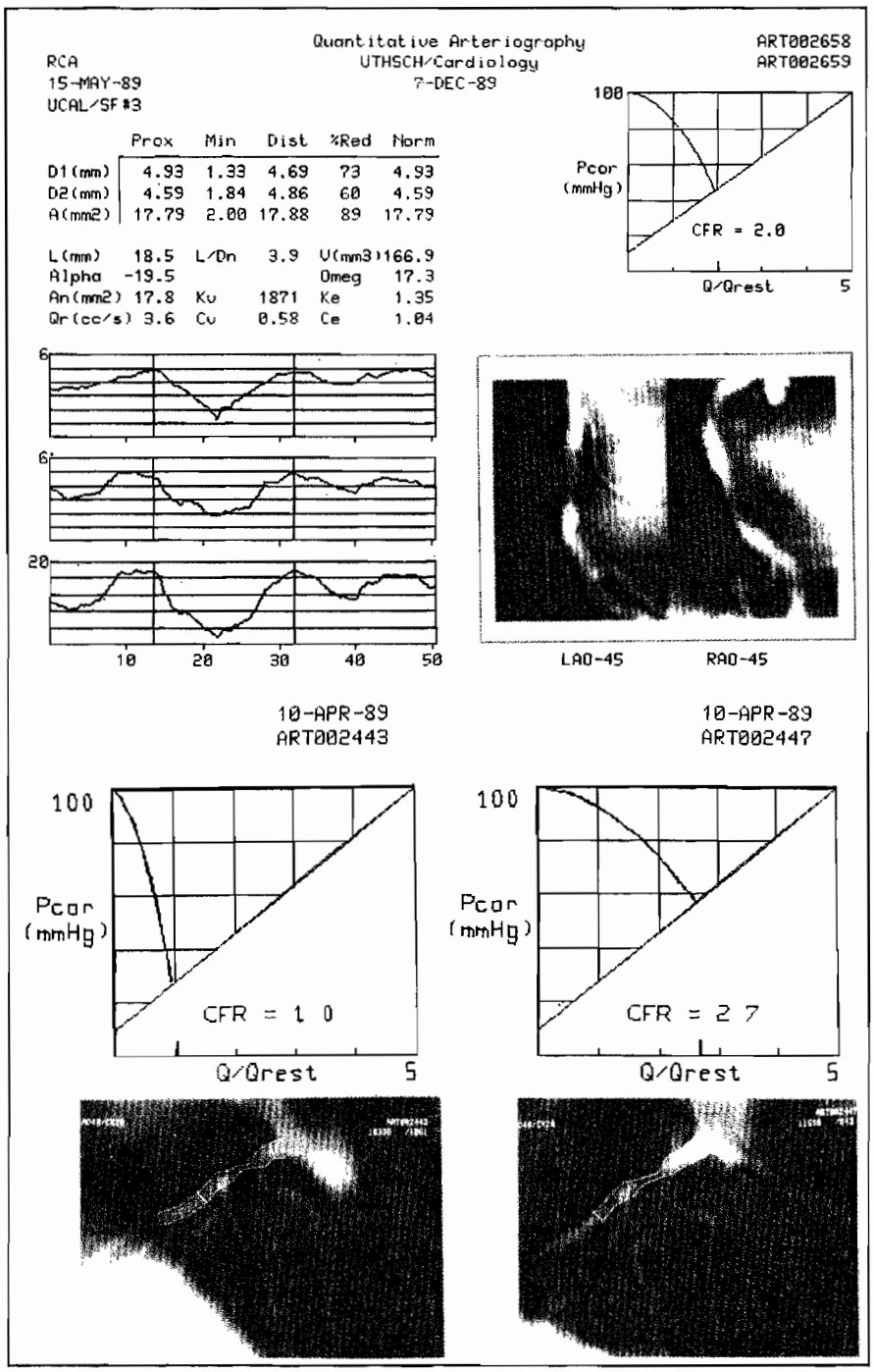

FIGURE 1. ***Top,*** **quantitative arteriographic data for each patient showing stenosis dimensions including minimal (Min), proximal (Prox) and distal (Dist) absolute lumen diameters, percent diameter stenosis in each view (D_1, D_2), minimal, proximal and distal cross-sectional lumen area and percent area stenosis, volume, length, area-length of the stenosed segment, entrance and exit angles, and fluid dynamic coefficients characterizing viscous and expansion losses (Cv, Ce, Kv and Ke)** ***(upper left). Lower left graphs*** **show diameters in 2 views and cross-sectional lumen area as functions of axial position. The** ***graph*** **on the** ***upper right*** **shows determination of stenosis coronary flow reserve (CFR). The** ***upward slanting, straight diagonal line*** **representing maximal arteriolar vasodilation in the absence of a stenosis crosses the downward curving pressure-flow relation characteristic of the stenosis. Stenosis flow reserve in this example is 2.0, determined as the maximal flow relative to resting flow (Q/Qrest) for a given stenosis geometry under standardized hemodynamic conditions of 100 mm Hg aortic pressure and normal stenosis flow reserve of 5.** ***Bottom,*** **2 sequential studies showing regression with improvement in stenosis flow reserve from 1.0 to 2.7. LAO = left anterior oblique; Norm = normal; RAO = right anterior oblique.**

ic conditions.[2,7,21] The 95% confidence interval for stenosis flow reserve was ± 0.66, with a reproducibility of primary dimensions of ± 3 to ± 5%.[2,4-7,19-21] The advantages of measuring stenosis flow reserve compared with single stenosis dimensions such as percent stenosis mentioned before have been discussed in detail elsewhere.[2-10,19-21]

Our quantitative arteriographic method is similar to that of Brown et al,[22,23] but was developed independently and in parallel using automated border recognition rather than visual tracing to determine stenosis dimensions.[2,5-7,19-21] It also differs by taking into account length-dependent exit effects not previously accounted for, and determines stenosis flow reserve as a single integrated measure of stenosis severity taking into account all stenosis dimensions.

Because different stenosis dimensions often change in opposite directions, the definitions of progression, regression and molding of stenoses are necessary. Figure 2 illustrates what we have termed simple regression in which all primary dimensions of proximal, minimal and distal diameters improve, the exit angle becomes smaller or more streamlined, percent diameter narrowing decreases and stenosis flow reserve increases. In simple progression all of these measurements become worse.

Figure 3 shows more complex changes in which (top panel) proximal and distal diameters worsen (progression), the narrowest segment remains unchanged (stabilization or no progression), while percent diameter lessens and stenosis flow reserve increases reflecting overall improvement or diminution in severity (regression). The middle panel of Figure 3 shows worsening of distal and proximal diameters, enlargement or regression of the narrowest segment, lessening of percent diameter stenosis with more improvement in stenosis flow reserve. We term this pattern remolding or a shape change of the stenosis that leaves a diffusely narrower artery than normal but with less segmental narrowing and improved flow capacity. Because overall flow capacity or stenosis flow reserve is improved, this pattern of remolding is characteristic of regression. The lowest panel of Figure 3 shows narrowing of proximal and distal segments to a greater extent than the narrowest segment, thereby causing improved, less severe percent diameter stenosis, but stenosis flow reserve or flow capacity is worse, a pattern that is one form of remolding with progression of disease.

Data analysis: Individual stenosis dimensions were analyzed as continuous variables from the first to the second arteriogram within the treatment, control or subgroups with standard 2-tailed, paired *t* tests comparing arteriograms at entry to follow-up arteriograms[24] and with unpaired *t* tests[24] and analysis of variance[1] for comparisons between control and treated or subgroups. Because significance and conclusions were the same by analysis of variance and by *t* testing, the latter are reported here since they are more familiar to most readers.

In the initial report of this trial using percent stenoses as the primary end point,[1] between-group comparisons included coronary lesions that progressed to total occlusion during the year since such an event is an important clinical end point. Because the current report focuses on changes in stenosis geometry, those stenoses that progressed to occlusion, or occluded arteries that opened during the trial in both control and treatment groups (a total of 6 of 198 stenoses), were excluded from analysis in this report. This exclusion was necessary because potentially large incremental changes due possibly to thrombosis or thrombolysis could bias mean values of shape change due to atheromatous alterations in other stenoses. Analysis of all data including stenoses progressing to occlusion or occluded arteries opening during the trial showed greater, more significant differences between control and treated groups but was not different from the more conservative results excluding those instances, as reported later. Of 48 patients enrolled, 7 did not have follow-up angiographic data[1] and 1 additional patient was excluded because the only end point was a total occlusion that became patent. Therefore the data base for this report is 40 patients.

RESULTS

In all, 40 patients having 192 stenoses, or 4.8 stenoses per patient, were analyzed, with 18 patients having

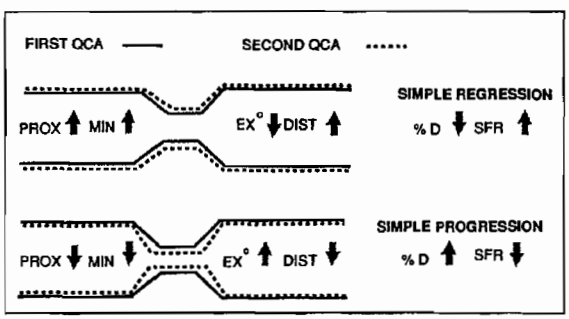

FIGURE 2. Patterns of changing coronary artery stenoses. DIST = distal diameters; % D = percent diameter stenosis; EX° = exit angle; MIN = minimum; PROX = proximal; QCA = quantitative coronary arteriography showing simple progression and regression; SFR = stenosis flow reserve accounting for all stenosis dimensions.

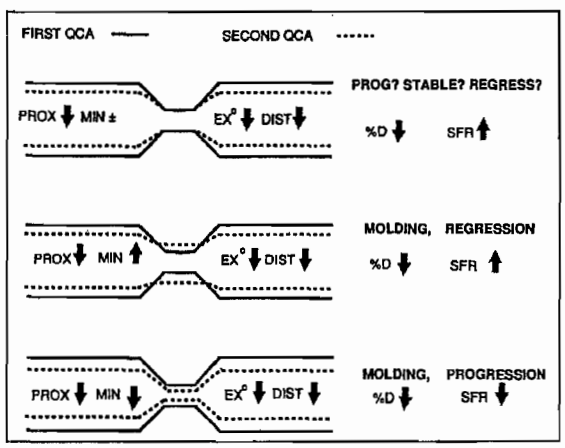

FIGURE 3. Patterns of changing coronary artery stenoses. Complex changes of stenosis dimensions in opposite directions with shape change or remolding during progression (PROG) or regression. Abbreviations as in Figure 2.

TABLE I Stenosis Dimension Changes

	PROX (mm)	MIN (mm)	EX° (deg.)	DIST (mm)	% DS	SFR
Control Subjects (87 stenoses)						
QCA1	3.07	1.75	12.7	2.84	42.7	3.90
QCA2	2.98	1.64	14.0	2.71	44.4	3.79
ΔQCA 2-1	−0.10	−0.12	+1.14	−0.14	+1.75	−0.11
p for Δ	0.01	0.001	NS	0.000	NS	NS
Treated Subjects (105 stenoses)						
QCA1	2.86	1.67	16.0	2.67	40.1	3.94
QCA2	2.78	1.67	16.1	2.55	38.0	4.07
ΔQCA 2-1	−0.08	+0.007	−0.91	−0.11	−2.1	+0.13
p for Δ	0.02	NS	NS	0.001	0.03	0.03
p for ΔT vs ΔC	NS	0.008	NS	NS	0.006	0.01

C = control; deg. = degree; % DS = percent diameter stenosis; DIST = distal diameter just distal to stenosis; EX° = exit angle; MIN = minimal diameter at narrowest point; NS = not significant; PROX = proximal diameter just proximal to stenosis; QCA = quantitative coronary arteriography; SFR = stenosis flow reserve; T = treated.

TABLE II Baseline Severity and Stenosis Dimension Changes

	PROX (mm)	MIN (mm)	EX° (deg.)	DIST (mm)	% DS	SFR
Mild, Control (74 stenoses)						
QCA1	3.15	1.91	12.2	2.94	38.2	4.26
QCA2	3.04	1.78	13.7	2.82	40.8	4.07
ΔQCA 2-1	−0.11	−0.14	+1.47	−0.12	+2.6	−0.19
p for Δ	0.015	0.001	NS	0.004	0.015	0.011
Mild, Treated (88 stenoses)						
n = 88						
QCA1	2.83	1.81	10.7	2.65	35.0	4.33
QCA2	2.76	1.78	10.2	2.55	34.3	4.32
ΔQCA 2-1	−0.06	−0.03	−0.54	−0.09	−0.7	−0.01
p for Δ	NS	NS	NS	0.006	NS	NS

Mild = baseline stenosis flow reserve ≥3; other abbreviations as in Table I.

TABLE III Baseline Severity and Stenosis Dimension Changes

	PROX (mm)	MIN (mm)	EX° (deg.)	DIST (mm)	% DS	SFR
Severe, Control (13 stenoses)						
QCA1	2.59	0.82	15.7	2.30	68.4	1.82
QCA2	2.60	0.89	15.7	2.12	65.1	2.17
ΔQCA 2-1	+0.00	+0.06	−0.05	−0.17	−3.3	+0.35
p for Δ	NS	NS	NS	NS	NS	NS
Severe, Treated (17 stenoses)						
QCA1	3.06	0.96	16.3	2.79	66.5	1.94
QCA2	2.87	1.14	12.7	2.55	57.2	2.79
ΔQCA 2-1	−0.19	+0.17	−3.6	−0.24	−9.3	+0.85
p for Δ	0.014	0.002	NS	0.048	0.001	0.000

Severe = baseline stenosis flow reserve <3; other abbreviations as in Table I.

87 coronary artery stenoses in the control group and 22 patients having 105 stenoses in the treated group. The mean interval between the first and second arteriogram was 15 ± 3 months as either a control or treatment subject.

Table I lists the dimension changes in control and treated groups with the statistical significance of each change. Figure 4 illustrates these changes and the statistical significance of the difference in each dimensional change between the control and treated subjects. In both groups, both proximal and distal diameters significantly decreased. The minimal diameter decreased further or progressed in controls but did not progress in the treated group. Percent diameter stenosis and stenosis flow reserve worsened somewhat in the control subjects, although not significantly, improved significantly in the treated group, and the changes from the first to the second study between the control and treated groups were statistically significant.

Tables II and III and Figure 5 show changes in stenosis dimensions for lesions that were initially mild (stenosis flow reserve ≥3) or initially severe (stenosis flow reserve <3) at the baseline entry study. For baseline mild lesions (Table II) in the control group, proximal, minimal, distal diameters, percent diameter stenosis and stenosis flow reserve all worsened significantly, reflecting simple progression of all dimensions. Baseline mild lesions in the treatment group remained stable with no change in proximal and minimal diameters, percent diameter stenosis and stenosis flow reserve, all indicating that progression was prevented; distal diameter decreased slightly but had little effect on flow reserve.

Baseline severe lesions in the control group showed no significant change during the study (Table III). Baseline severe lesions of the treated group showed mild, statistically significant, increased narrowing of proximal and distal diameters, enlargement of the minimal diameter, a decrease of −9.3% diameter stenosis units, and improved stenosis flow reserve, all indicating statistically significant improvement. These changes reflect remolding of the stenosis, with regression toward a diffusely smaller artery than normal, and having less segmental narrowing and improved flow capacity.

Figure 5 summarizes these changes in which statistically significant changes were seen on the second arteriogram compared with those seen at the entry study.

Figure 6 shows dimensional changes in relation to adherence to the risk modification program for all patients in the combined control and treated groups classified according to severity of baseline stenosis at the ini-

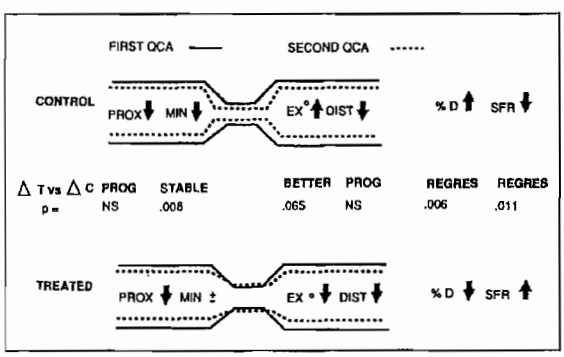

FIGURE 4. Comparison of stenosis dimensional changes (Δ) from initial (QCA, *solid line*) to follow-up (QCA, *dashed line*) arteriograms between control and treated groups.
ΔC = change in the control group; NS = not significant; REGRES = regression; ΔT = change in treated group; ± = no change; other abbreviations as in Figure 2.

tial entry study. For this analysis, the combined groups were divided into subgroups of poor adherence (adherence score of ≤0.75), good adherence (adherence score of >0.75 but ≤1.15) and those that excelled in risk factor management (adherence score of >1.15) where adherence measures were derived by dividing indexes of prescribed behavioral changes into the measured changes as described previously.[1]

Baseline mild lesions (stenosis flow reserve ≥3, Figure 6A) in the poor adherence group showed statistically significant progression of all dimensions, whereas groups with good and excellent adherence showed no progression. Baseline severe lesions (stenosis flow reserve <3, Figure 6B) in the poor and good adherence groups remained stable without further progression. Baseline severe stenoses in the group that excelled in

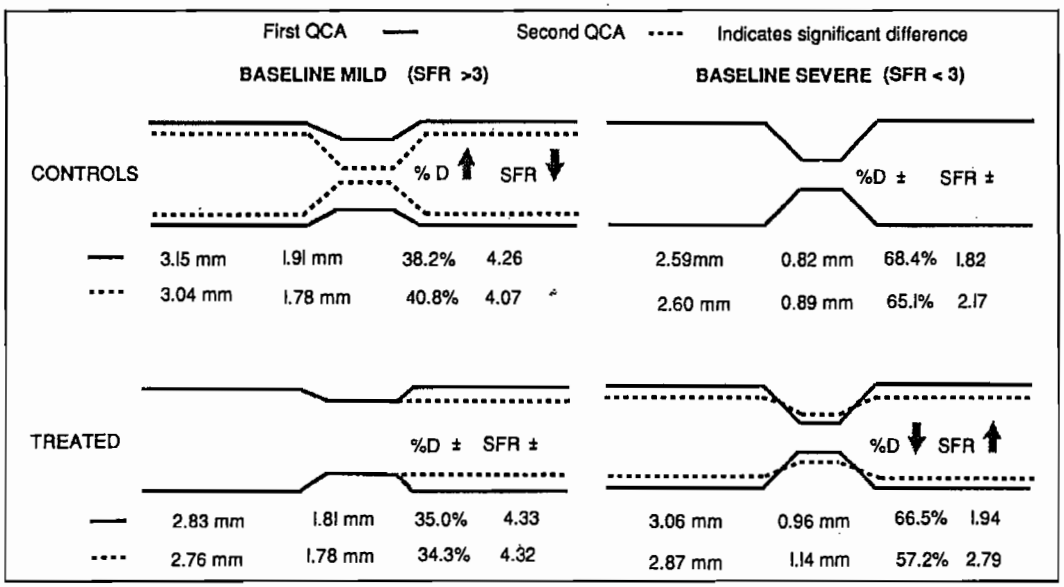

FIGURE 5. Stenosis change related to baseline severity in treated and control groups. Abbreviations as in Figure 2.

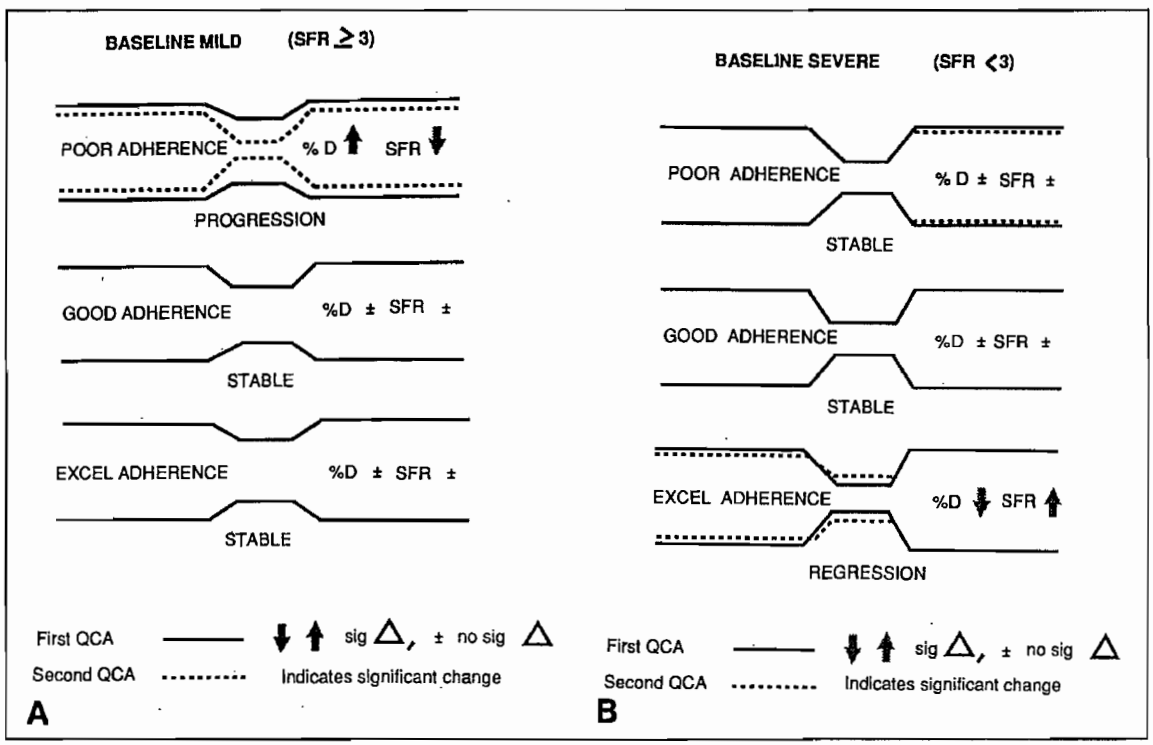

FIGURE 6. Stenosis change related to both baseline severity and adherence to the program of risk modification for mild baseline stenoses with stenosis flow reserve ≥3 *(A)* and for severe baseline stenoses with stenosis flow reserve <3 *(B)*. EXCEL = excellent; sig = significant; other abbreviations as in Figure 2.

TABLE IV Comparison of Methods, Sample Size, Outcome of Coronary Artery Disease Regression Trials

Study	End Points and Methods	No. of Subjects	p Value for End Point (Rx vs C)	End Points or End Point Change		% Δ Total Cholesterol (Rx-C)
				Control	Treated	
MRFIT[32]	Cardiac events, 1° prevention	12,866	NS	1.9%	1.8%	1.5%
Frick[33]	Cardiac events, 1° prevention	4,081	0.02	4.1%	2.7%	8.5%
CDP[34]	Cardiac events, 2° prevention	8,341	NS	26%	23%	10%
Carlson[35]	Cardiac events, 2° prevention	555	0.01	26%	17%	13%
CLAS[17]	Arteriog. score, visual estim.	162	0.001	0.5		22%
FATS[18]	% DS, visual borders	142	0.017	5.9% DS		29%
LHT[1,2]	% DS, automated	42	0.001	8.4% DS		20%
	Stenosis flow reserve		0.000	0.5		

For 1° and 2° prevention trials, end point = coronary artery disease events/no. of patients in each group; for arteriography end point = difference between controls (C) and treated group (Rx) in stenosis severity of study 1–study 2 of severe stenoses (> 50% DS or SFR > 3%).
Arteriog. = arteriography; CDP = Coronary Drug Project; % DS = % diameter narrowing of severe stenoses (> 50% or SFR > 3%); CLAS = Cholesterol-Lowering Atherosclerosis Study; estim. = estimated; FATS = Familial Atherosclerosis Treatment Study; LHT = Lifestyle Heart Trial; MRFIT = Multiple Risk Factor Intervention Trial; SFR = stenosis flow reserve.

adherence to the program showed statistically significant regression of minimal diameter, percent diameter stenosis and stenosis flow reserve. Therefore, good adherence to the lifestyle program prevented progression of milder stenoses, but more vigorous adherence was required for regression of severe coronary artery stenoses.

If the absolute dimension changes reported here are expressed as a percent change from baseline as in previous papers, the regression becomes even more apparent. For example, for severe baseline stenoses (stenosis flow reserve <3), the minimal diameter increased by a change of + 0.17 mm compared with a mean minimal absolute diameter of 0.96 mm at baseline, an approximately 18% improvement. In this same group, the percent diameter stenosis change was −9.3% stenosis diameter units from a mean baseline severity of 67% diameter narrowing, or a 14% improvement, with a t value of 4.05 and p value of 0.001. By comparison in this group, stenosis flow reserve improved by a change of + 0.85 over a baseline stenosis flow reserve at entry of 1.9, or a 45% improvement in stenosis flow reserve, with a larger t value of 5.11 and a p value of <0.0000. Therefore, the statistical significance of the changes in this study were greater for the integrated measure of severity than for the single measure of percent stenosis, although both showed significant improvement in the treated group.

Statistical analysis of stenoses as opposed to patients was performed because multiple stenoses in a patient showed changes essentially independent of each other as previously demonstrated.[1] Statistical analysis weighting for the small degree of within-patient-correlation of stenosis changes as previously described[1] did not change the significance of these results. Analysis was also performed on a per-patient basis by averaging all percent diameter stenoses for each patient and classifying patients according to threshold diameter stenosis unit changes of: ≥+10% for progression, ≤−10% for regression, and <±10% as no significant change, similar to Brown et al.[18] By this per patient analysis, 40% more of treated patients showed regression compared with control subjects, a statistically significant difference. However, we emphasize that this approach does not take into account the complex shape changes observed.

TABLE V Cholesterol and Coronary Artery Disease Regression in Arteriographic Trials

Study	Percent Change TC Rx–Control (%)	Arteriog. Reg.
Cohn[15]	6%	0
NHLBI[16]	17%	0
Nikkila[14]	18%	0
Nash[13]	18%	0
CLAS[17]	22%	16%
FATS[18]	29%	36%*
LHT[1,2]	20%	41%*

*Percentages of patients with > 10% diameter stenosis units of regression.
Arteriog. = arteriographic; Reg. = regression; Rx–Control = differences between treated and control groups; TC = total cholesterol; other abbreviations as in Table IV.

DISCUSSION

This study demonstrates that vigorous modification of multiple risk factors stops progression of mild to moderate coronary artery stenoses and causes regression of severe stenoses, leaving residual milder diffuse narrowing of the artery with less severe segmental stenoses and improved flow reserve. Complex shape changes or remolding of coronary stenoses occur with progression or regression so that no single anatomic dimension alone describes all of the geometric changes seen.

Significance of changes in stenosis shape: Although the number of patients in the study were small compared with previous reports, mean absolute changes of stenosis dimensions were statistically significant and internally consistent from several points of view. There was a dose effect of risk factor modification for preventing progression of mild stenoses and more stringent risk factor modification causing regression of severe stenoses. Severe stenoses showed greater regression than milder ones, reflecting a reasonable theoretical expectation that removal of a small amount of cholesterol from a severe stenosis having a small circumference would cause more improvement than the same amount of cholesterol removed from a mild stenosis having a large circumference. Published studies on experimental reversal report persistence of fibrosed, diffusely narrowed coronary arteries having less segmental narrowing in

treated groups compared with control subjects.[25–28] There are also different rates of progression/regression of different parts of atherosclerotic arteries in opposite directions depending on their histologic maturity and the duration/degree of serum/dietary cholesterol changes.[26–29] Finally, because coronary blood flow effects are a function of arterial radius raised to the fourth power, small changes in radius have proportionately much larger effects on the flow capacity and functional severity of stenoses, thus contributing to the greater significance of stenosis flow reserve as a measure of change in severity.

Comparison with other studies: Table IV compares representative primary and secondary intervention trials with the recent arteriographic randomized trials. In the spectrum of end point measures, from cardiac events to automated quantitative coronary arteriography for stenosis flow reserve, more quantitative or complete analysis of stenosis geometry, or both, yielded significant differences in end points with smaller numbers of subjects. Thus, the physiologic measure of severity (stenosis flow reserve accounting for the integrated total effects of all dimensional changes) shows statistical significance between treated and control groups with smaller numbers of study subjects than for other end points measured (Table IV).

Clinical implications: More stringent or vigorous treatment with lipid-lowering regimens[1,2,18] than conventionally used[30,31] appear necessary to achieve significant improvements in stenosis severity of treated versus control groups (Table V). The control groups of the most recent studies[1,17,18] following approximately the standard dietary guidelines of the American Heart Association[30] and National Cholesterol Education Program[31] showed high prevalence of progression.

Patients with coronary artery disease frequently have total cholesterol, and low- and high-density lipoprotein cholesterol levels that fall within the normal range, as were the average cholesterol levels in the Lifestyle Heart Trial.[1] However, in this study stringent dietary fat restriction and reduction of serum cholesterol substantially below "normal" levels were associated with the cessation of progression or regression of stenosis by quantitative coronary arteriography. The control group with average cholesterol levels within the normal range showed progression of coronary artery stenosis. Although not clearly defined, there may be a variable susceptibility to coronary atherosclerosis for given level of risk factor exposure and an important role of dietary fat separate from serum cholesterol. Many men with risk factors appear resistant to coronary artery disease despite risk factors or excess dietary fat, or both, whereas others are susceptible to even modest risk factors. In patients with coronary artery disease and normal cholesterol levels, vigorous reduction of dietary fat and reduction in cholesterol levels to substantially below "normal" ranges is associated with cessation of progression or regression of disease.

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