

# Effects of Intensive Multiple Risk Factor Reduction on Coronary Atherosclerosis and Clinical Cardiac Events in Men and Women With Coronary Artery Disease

## The Stanford Coronary Risk Intervention Project (SCRIP)

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**Background** Recent clinical trials have shown that modification of plasma lipoprotein concentrations can favorably alter progression of coronary atherosclerosis, but no data exist on the effects of a comprehensive program of risk reduction involving both changes in lifestyle and medications. This study tested the hypothesis that intensive multiple risk factor reduction over 4 years would significantly reduce the rate of progression of atherosclerosis in the coronary arteries of men and women compared with subjects randomly assigned to the usual care of their physician.

**Methods and Results** Three hundred men (n=259) and women (n=41) (mean age, 56±7.4 years) with angiographically defined coronary atherosclerosis were randomly assigned to usual care (n=155) or multifactor risk reduction (n=145). Patients assigned to risk reduction were provided individualized programs involving a low-fat and -cholesterol diet, exercise, weight loss, smoking cessation, and medications to favorably alter lipoprotein profiles. Computer-assisted quantitative coronary arteriography was performed at baseline and after 4 years. The main angiographic outcome was the rate of change in the minimal diameter of diseased segments. All subjects underwent medical and risk factor evaluations at baseline and yearly for 4 years, and reasons for all hospitalizations and deaths were documented. Of the 300 subjects randomized, 274 (91.3%) completed a follow-up arteriogram, and 246 (82%)

had comparative measurements of segments with visible disease at baseline and follow-up. Intensive risk reduction resulted in highly significant improvements in various risk factors, including low-density lipoprotein cholesterol and apolipoprotein B (both, 22%), high-density lipoprotein cholesterol (+12%), plasma triglycerides (-20%), body weight (-4%), exercise capacity (+20%), and intake of dietary fat (-24%) and cholesterol (-40%) compared with relatively small changes in the usual-care group. No change was observed in lipoprotein(a) in either group. The risk-reduction group showed a rate of narrowing of diseased coronary artery segments that was 47% less than that for subjects in the usual-care group (change in minimal diameter,  $-0.024 \pm 0.066$  mm/y versus  $-0.045 \pm 0.073$  mm/y;  $P < .02$ , two-tailed). Three deaths occurred in each group. There were 25 hospitalizations in the risk-reduction group initiated by clinical cardiac events compared with 44 in the usual-care group (rate ratio, 0.61;  $P = .05$ ; 95% confidence interval, 0.4 to 0.9).

**Conclusions** Intensive multifactor risk reduction conducted over 4 years favorably altered the rate of luminal narrowing in coronary arteries of men and women with coronary artery disease and decreased hospitalizations for clinical cardiac events. (*Circulation*. 1994;89:975-990.)

**Key Words** • angiography • cholesterol • diet • exercise • clinical trials

Quantitative arteriography has been used increasingly to evaluate the effects of various treatments on the progression of atherosclerosis in coronary arteries. These angiographic trials achieve adequate statistical power with a substantially smaller sample size and trial duration compared with trials using clinical cardiac events as primary end points. Studies using clinical or angiographic end points usually

have evaluated single-factor interventions, with most studies modifying plasma lipoprotein concentrations using single or multiple drug therapy<sup>1-8</sup> or ileal bypass surgery.<sup>9</sup> Treatments that significantly lowered low-density lipoprotein cholesterol (LDL-C), with and without significant increases in high-density lipoprotein cholesterol (HDL-C), generally have reduced the rate of fatal and nonfatal cardiac events,<sup>1-3</sup> diminished coronary artery narrowing (disease progression), and increased artery diameter (disease regression) in selected patients.<sup>4-9</sup> Calcium channel blocker use has not significantly altered artery diameter where advanced atherosclerotic lesions existed but is reported to decrease the formation of new lesions.<sup>10,11</sup>

Multiple risk factor intervention has been tested using clinical outcomes in the Multiple Risk Factor Intervention Trial<sup>12</sup> and using arteriographic end points in two multifactor, lifestyle risk-reduction trials.<sup>13,14</sup> In one trial, an exceptionally low-fat, low-cholesterol diet

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along with moderate exercise, smoking cessation, and stress management resulted in a reduced rate of coronary artery narrowing over 1 year in 22 patients selecting the risk-reduction program versus 19 patients selecting usual care.<sup>13</sup> In the other study, patients assigned to a low-fat, low-cholesterol diet and vigorous exercise training for 1 year demonstrated less disease progression than patients assigned to usual care.<sup>14</sup> Recently, plasma cholesterol reductions over 39 months by diet alone or diet plus cholesterol-lowering medication were associated with less disease progression and more regression than that observed in control subjects.<sup>15</sup> No studies have evaluated the combined impact of comprehensive lifestyle changes and lipid medications on the progression of coronary atherosclerosis.

The Stanford Coronary Risk Intervention Project (SCRIP) tested the hypothesis that intensive multifactor risk reduction including changes in lifestyle and lipid-lowering medications for 4 years would significantly reduce the rate of narrowing of the minimal diameter of coronary artery segments with angiographically visible atherosclerotic lesions compared with changes in similar segments in subjects receiving their own physician's usual care. Secondary questions included the comparison of changes in the mean diameter and percent stenosis of visibly diseased segments, the minimal and mean diameters of visibly normal segments, the proportion of patients showing disease progression or regression, and clinical cardiac events.

## Methods

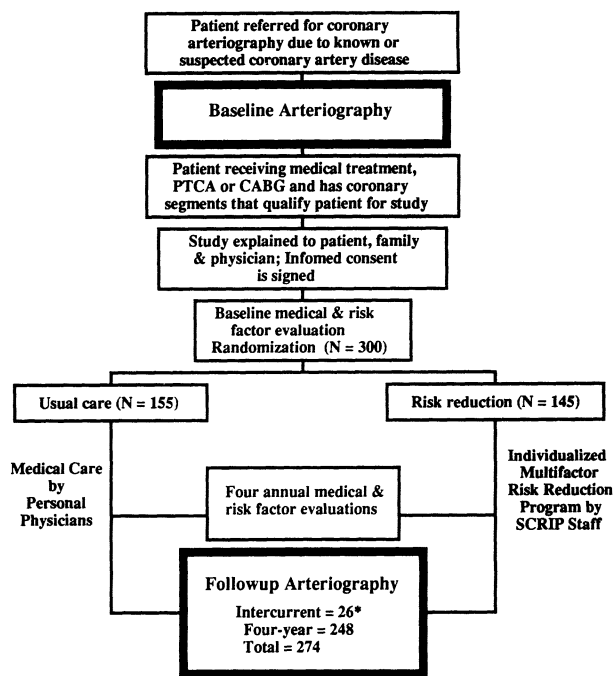
### Study Design

This study was a randomized trial of 300 subjects who were referred to one of four local hospitals for coronary arteriography between February 1984 and March 1987. Consecutive potentially eligible subjects received arteriography and, if still eligible, had the full study protocol explained and signed an informed consent form. After baseline evaluations, subjects were randomized to the usual care of their own physician or to an individualized, multifactor, risk-reduction program managed by the SCRIP staff in cooperation with the patient's personal physician (Figure). All subjects were scheduled for four annual medical and risk factor evaluations and follow-up coronary arteriography at the fourth year. The study protocol and progress were reviewed before the start and annually by the Stanford University Panel on Human Subjects in Medical Research, by committees on the use of human subjects at each of the participating hospitals, and by an external Safety and Data Monitoring Committee appointed by the National Heart, Lung, and Blood Institute.

### Subjects

#### Eligibility

Patients were screened for study eligibility at the time of clinically indicated coronary arteriography at the four participating hospitals (Stanford University Hospital, Palo Alto Veterans Administration Hospital, Sequoia Hospital in Redwood City, Calif, and Good Samaritan Hospital in San Jose, Calif). Men and women less than 75 years of age who lived within a 5-hour drive of Stanford University were eligible if free of severe congestive heart failure, pulmonary disease, intermittent claudication, or noncardiac life-threatening illness and were considered capable of following the study protocol (Table 1). After arteriography, patients were treated medically, received percutaneous transluminal coronary angioplasty (PTCA), or had coronary artery bypass graft surgery (CABG), in accordance with clinical indications. Subjects remained eligible for the study if at least one major coronary



\* Clinically indicated arteriogram between 12 and 42 months post-baseline

Study design for Stanford Coronary Risk Intervention Project (SCRIP). The change in coronary lumen dimensions from baseline to follow-up arteriography compared between the usual-care and risk-reduction groups provides the primary outcome data. PTCA indicates percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft surgery.

artery had a segment with lumen narrowing between 5% and 69% that was unaffected by revascularization procedures. Subjects were excluded if they had no qualifying segments, the arteriography was unsatisfactory for quantitation, a medical complication occurred during angiography, the patient had a left ventricular ejection fraction of less than 20%, or the patient was in another research study.

### Recruitment

After eligibility was confirmed, permission to recruit subjects was obtained from the subject's cardiologist and primary care physician. Eligible subjects (n=538) were given a detailed description of the study, including the need for repeat arteriography. A signed consent form was obtained from 300 subjects (56% of those eligible). The others (n=238) declined to participate because of lack of interest or time, reluctance to undergo repeat arteriography, or family or physician advice.

### Clinical Measurements

All subjects had their clinical status and cardiac risk factors evaluated at baseline before randomization and annually for 4 years. At baseline, clinic visits occurred at least 3 weeks after hospital discharge. The staff collecting data in the clinic were not blinded to group assignment of subjects, but all laboratory measurements were performed by staff blinded to group assignment.

Blood pressure was measured three times after a 5-minute rest and with the subject seated using a Hawksley random-zero sphygmomanometer with an average of the last two values used for study purposes. Skinfolds were measured in triplicate at the subscapula, triceps, and suprailliac crest and summed to represent general adiposity. Reported smoking status was verified by measuring the carbon monoxide content of expired air using an Ecolyzer<sup>16</sup> and the thiocyanate concentration in plasma.<sup>17</sup> Symptom-limited treadmill exercise testing was performed using a Balke-type protocol with continuous monitoring of a three-lead ECG and recording of a 12-lead ECG;

**TABLE 1. Subject Recruitment Including All Patients Screened at Participating Hospitals During Study Enrollment**

	No. of Patients
Patients screened	4771
Reasons for ineligibility before angiography	
Angiography for reasons other than CAD	
Cardiac transplant evaluation	212
Myopathy	124
Arrhythmia	252
Valvular	520
Non-CAD heart disease	165
No qualifying segment before catheterization	532
Personal factors	
Age >75 y	407
Live out of area	607
Moving from area	22
Other life-threatening illness	138
Severe COPD/CHF/ claudication	188
Psychosocial problems	145
Non-English speaking	37
Postangiographic exclusions	
Unsatisfactory for quantitation	95
In other studies	38
Ejection fraction <20%	13
No qualifying, nonrevascularized segment (5% to 69% lumen narrowing)	559
Normal arteries	220
Catheterization complication	29
Total ineligible	4233
No. of eligible patients, % of patients screened	538 (11.3%)
Eligible but refused	
Refused repeat angiogram	28
Physician recommendation	14
Other patient reasons	196
Total refused	238
No. of eligible, consented, and randomized patients, % of patients eligible	300 (56%)

CAD indicates coronary artery disease; COPD, chronic obstructive pulmonary disease; and CHF, congestive heart failure.

blood pressure; and signs, symptoms, and rating of perceived exertion at the end of each stage of exercise, at peak exercise, and periodically during 7 minutes of recovery.

At baseline and annually, fasting plasma lipids and lipoproteins were measured during two clinic visits, usually within 2 weeks of each other. The two values were averaged for each subject to represent the subject at baseline and for each year in the study. On one of these visits, plasma total cholesterol (TC),

HDL-C, and triglycerides (Tg) were measured and LDL-C was calculated in millimoles per liter using the formula  $LDL-C = TC - (HDL-C + Tg/2.18)$ .<sup>18</sup> However, if the level of Tg exceeded 3.39 mmol/L, very-low-density lipoprotein cholesterol (VLDL-C) was measured by enzymatic methods<sup>19</sup> after ultracentrifugation for 18 hours.<sup>20</sup> On the other visit, LDL-C was directly measured after separation by ultracentrifugation.<sup>21</sup> Plasma concentrations of TC and Tg were measured in the Stanford Lipoprotein Research Laboratory by enzymatic procedures (ABA 200 instrument, Abbott Laboratories).<sup>19,20</sup> HDL-C was measured by dextran sulfate-magnesium precipitation<sup>22</sup> followed by enzymatic determination of cholesterol.<sup>20</sup> The laboratory remained certified by the Centers for Disease Control and Prevention lipid standardization program throughout. Blood samples also were analyzed for lipoprotein subfractions at the Lawrence Berkeley Laboratories, and these results will be reported separately.

For measurement of lipoprotein(a) [Lp(a)] and LDL plus intermediate-density lipoprotein (IDL) apolipoprotein B (apo B),  $d < 1.006$  g/mL lipoproteins were separated by ultracentrifugation,<sup>23</sup> and the infranant was collected and stored at  $-70^{\circ}\text{C}$  for subsequent analysis. Lp(a) concentration was measured with an enzyme-linked immunosorbent assay (ELISA) kit [Macra Lp(a) Terumo Diagnostics Division] as described previously.<sup>24,25</sup> The assay uses a monoclonal capture antibody immunospecific to apo(a) and a peroxidase-conjugated polyclonal detection antibody with recognition of the entire Lp(a) molecule. The antibodies show no detectable cross-reactivity with plasminogen. LDL plus IDL apo B was measured by standardized ELISA<sup>26</sup> using two monoclonal capture antibodies (Medix Biotech). Biotinylated LDL was used as the lipoprotein competitor, and concentration measurements were made by addition of streptavidin-conjugated peroxidase. Lipoprotein calibrators were standardized using CDC #1883 serum reference material (Centers for Disease Control and Prevention) and pooled reference sera (Northwest Lipid Research Clinic). Plasma glucose concentration was measured using the glucose oxidase method,<sup>27</sup> and insulin concentration was measured by radioimmunoassay.<sup>28</sup>

Dietary intake was determined by 4-day food records (Thursday through Sunday) using the Nutrition Coordinating Center protocols for data collection and coding and version 13 database for data analysis.<sup>29</sup> Participants were instructed and their records were reviewed in-person by trained diet coders. Physical activity was reported using the 7-day physical activity recall<sup>30</sup> and other questions that solicited information on the frequency of participating in specific leisure-time and conditioning activities. At each visit, current medication use was obtained by interview as was information on hospitalizations or other medical care received during the past year. Patient records were obtained for all hospitalizations.

## Angiographic Measurements

### Baseline Arteriography

During the recruitment phase of the study, all patients having diagnostic coronary arteriography at participating hospitals who met the general clinical profile for SCRIP had baseline coronary arteriograms performed in a uniform manner by the patient's own attending physician. Sublingual nitroglycerin was administered 3 to 5 minutes before the angiography. Coronary catheters with tantalum metallic cylindrical markers near their distal end provided a sharp calibration edge for quantitation, which reduces measurement variation when using computer-assisted measurement techniques.<sup>31</sup> High-quality intensifiers with a 6- to 7-in. magnification mode were used for imaging, with table panning limited to the plane perpendicular to the path of the x-ray beam. A menu of specified projections for both left and right coronary artery recordings was provided; however, angiographers often selected additional views that optimally visualized all portions of the coronary vessels. Angiographers were generally blinded to group assignment of subjects.

### Coronary Segmentation

Coronary vessels were divided into one or more segments varying in length from 0.5 to 3.5 cm. The coronary segments were defined on the baseline arteriogram and included all assessable portions of coronary vessels that exceeded 1.5 mm in diameter. To ensure comparable measurement of the "quantitation segments" on serial arteriograms, segments were defined by either proximal or distal fiducial points (typically a vessel branch) and by absolute length. Adequate segment visualization in a projection that avoided foreshortening was required.

### Definition of a Qualifying Segment

SCRIP required qualifying segments to be at least 0.5 cm long, the maximum diameter to be well visualized and adequate for quantitation, that neither the qualifying segment nor any vessel proximal to it contain a lesion  $\geq 70\%$  in diameter reduction, and that no portion of the vessel had been grafted or instrumented by a prior revascularization procedure. Segments containing lesions  $\geq 70\%$ , although clinically important, yield potentially misleading results during follow-up because a substantial proportion are already causing symptoms that lead to revascularization. Revascularization within 12 months after the baseline angiogram was often an outgrowth of the original angiographic findings rather than the result of an intercurrent angiogram documenting disease progression. Only 2% (18 of 369) of vessels excluded from quantitation because of  $\geq 70\%$  narrowing would otherwise have been eligible for quantitation. Reasons for exclusion of vessels from contributing diseased segments for quantitation include lesion of 99% to 100% ( $n=123$ ); vessel revascularized before or within 12 weeks of arteriogram ( $n=141$ ); no segment quantifiable because of vessel crossings, burn-out, and other technical factors ( $n=33$ ); or vessel flow potentially affected by a severe proximal or distal lesion or by revascularization ( $n=54$ ). The small number of nonrevascularized segments with lesions  $\geq 70\%$  that met the above criteria have not been included in our analysis. These severe lesions were excluded from primary analysis because of nonquantifiable selection biases toward revascularization and, often, inadequate flow that precluded accurate quantitation. Moreover, the contribution of thrombus formation to luminal narrowing in severe stenoses does not necessarily reflect the effects of antiatherosclerosis interventions. Visually normal segments were quantitated; however, only those with visible coronary disease on the baseline angiogram were used for testing the primary hypothesis.

### Computer-Assisted Quantitation

A computer-assisted quantitation system was designed at Stanford University to measure coronary vessels on 35-mm cineangiograms. The system's design, accuracy, precision, and intraobserver and interobserver variabilities have been reported.<sup>32</sup> The system has two cine film digitizers that simultaneously process paired coronary arteriograms for evaluation of serial changes in coronary arteries.

Baseline and follow-up coronary angiograms were reviewed side-by-side on separate Siemens Cipro projectors with modified film illumination systems. The projection lenses of each were replaced by beam splitters, which allows each film to be viewed simultaneously by two video cameras. One is a standard format (525-line) CCD television camera that is used for real-time remote viewing of the cine film. The second camera is a Videk Megaplus that incorporates a CCD sensor with a resolution of 1300 pixels horizontally and 1030 pixels vertically. The image is digitized within the camera and transmitted digitally to the computer, eliminating image noise that might be introduced by the digitizing process. A computer-controlled shutter on the camera controls image exposure time using an iterative optimization algorithm applied to the selected area of interest in the image.

A pair of video monitors for each projector allows the operator real-time viewing of the film for frame selection. The

second monitor is connected to the image processor and is used for image analysis of selected regions of the film frame. Quantitation technicians who were blinded to subjects' group assignment preferentially selected end-diastolic frames; however, avoidance of vessel overlaps and the need for optimal visualization often necessitated selection of other diastolic frames. They used a mouse to approximate the edges of either the calibrating catheter or the coronary vessel. With these lines as initial search locations, the automatic edge-finding algorithm drew and then smoothed the edges, defining the edge as the combination of equal first and second derivatives of the gray scale density gradient, perpendicular to the long axis of the vessel. Known dimensions of the catheter markers were manually entered into the computer to permit calculation of the magnification factor.

All segment quantitations on serial films were based on identical projections and paired analyses. The operator selected the single plane that best visualized each segment and had the option of replacing short segments of computer-generated margins by manual tracing. For 72% of segments, this was not necessary and did not exceed 20% of the total length of any quantitated segment. For each quantitation segment, minimal and mean diameters were computed. For diseased segments, a reference diameter was defined by the operator to compute percent stenosis. Single-plane coronary quantitation was used because our prior observations indicated that mathematical algorithms that combined measurements obtained in two projections increased the coefficient of variation for individual lesion measurements and because of limitations in obtaining multiplanar orthogonal projections of proximal disease.

### Follow-up Arteriography

All consenting subjects had protocol-mandated follow-up arteriograms obtained 4 years after the baseline arteriogram with a permissible window of  $\pm 6$  weeks. Use of catheters with metallic markers, prior nitroglycerin administration, and replication of projection angles were performed as at the baseline study and at the same clinical site as the baseline angiogram. Subjects who required coronary arteriography for clinical reasons before the protocol-mandated 4-year study had their angiography performed in the same manner. In 8 subjects, a subsequent 4-year arteriogram was not obtainable. For these individuals, the results of earlier clinically indicated angiograms were included as long as the interval between the baseline and follow-up angiogram exceeded 12 months. If a subsequent revascularization procedure affected the "integrity" of the vessel containing a SCRIP-qualifying segment, only quantitation results for that segment up to the last available preprocedure angiogram were used. SCRIP-qualifying segments that were totally occluded on follow-up arteriography were imputed a minimal diameter of 0 mm and 100% stenosis. Segments distal to total occlusion were considered lost to follow-up.

### Randomization

After baseline data collection, subjects were stratified by the hospital at which they had their qualifying arteriogram and the clinically indicated treatment they received after this arteriogram: medical, PTCA, or CABG. Then, they were randomly assigned to the usual-care or the risk-reduction group. Randomization was performed using a random-numbers table with sequentially numbered, sealed opaque envelopes for each stratification category that were provided by the biostatistician. On receipt of a signed consent form, the appropriate envelope was opened, and group assignment was entered into a log book by an individual who had no contact with any SCRIP subject. At the completion of randomization, a comprehensive review of the log book and envelopes and verification of the stratification and randomization assignments were performed by the biostatistician. Group treatment categories were balanced with 72 (49%) of the 145 medically treated subjects assigned to the usual-care group, 74 (53%) of the 139

TABLE 2. Risk Factor Goals for Subjects Assigned to Risk-Reduction Group

Variable	Minimum	Intermediate	Maximum
Body weight, % ideal	110	105	100
SBP, mm Hg	<140	<130	≤120
DBP, mm Hg	<90	<85	≤80
Plasma cholesterol, mmol/L (mg/dL)	<5.69 (220)	<5.17 (200)	<4.65 (180)
LDL cholesterol, mmol/L (mg/dL)	<3.62 (140)	<3.23 (125)	<2.84 (110)
HDL cholesterol, mmol/L (mg/dL)	>1.16 (45)	>1.29 (50)	>1.42 (55)
Plasma triglycerides, mmol/L (mg/dL)	<1.81 (160)	<1.58 (140)	<1.13 (100)
Dietary fat, % calories	<30	<25	<20
Saturated fat, % calories	<10	<8	<6
Dietary cholesterol, mg/d	<250	<150	<75
P:S ratio*	≥1.0	≥1.0	≥1.0
Sodium, mg/d†	3000	3000	2500
Cigarette smoking, no. per day	<10	<5	0
Exercise capacity (METS)			
Men	>8	>10	>12
Women	>7	>8.5	>10
Fasting glucose, mg/dL	<110	<100	<90
1-Hr glucose, mg/dL	<200	<180	<160
Physical activity			
Routine aerobic, cal/d	+200	+300	+400
Training session, % MHR	50-75	60-75	70-85
	15- to 30-min sessions every other day	20- to 30-min sessions every other day	30- to 45-min sessions every other day

\*Emphasis was placed on achieving the desired percentage of calories from saturated fat, with P:S ratio approximately 1.0.

†Hypertensive participants were encouraged to reduce sodium further, with attention also given to other aspects of their diet.

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; P:S, polyunsaturated:saturated fat in diet; METS, multiple of resting energy expenditure; and MHR, maximal heart rate.

PTCA subjects assigned to the usual-care group, and 10 (63%) of the 16 CABG subjects assigned to the usual-care group. Stratification by hospital also resulted in equal distribution of subjects into the two groups and eliminated any bias resulting from differences in local patient care.

### Risk-Reduction Program

The risk-reduction goals established at the start of the study are summarized in Table 2. Emphasis was placed on each risk-reduction subject reaching the maximal goals, with the minimal and intermediate goals being applied selectively to enhance motivation and program adherence. Immediately after randomization, each risk-reduction subject met with a SCRIP nurse to design an individualized risk-reduction program based on the subject's risk profile, his or her motivation, and resources for making specific changes. Because many subjects lived more than 1 hour from Stanford University, nearly all risk-reduction activities were conducted using an individual rather than a group format.

All risk-reduction subjects were instructed by a dietitian in a low-fat, low-cholesterol, and high-carbohydrate diet with a goal of <20% of energy intake from fat, <6% from saturated fat, and <75 mg of cholesterol per day. Instructions to risk-reduction subjects were based on their baseline food records. A physical activity program was recommended consisting of an increase in daily activities such as walking, climbing stairs, and household chores and a specific endurance exercise training program with the exercise intensity based on the subject's treadmill exercise test performance. This exercise

program followed guidelines we developed previously for home-based exercise training of cardiac patients.<sup>33</sup> Current or recent ex-smokers were provided an individualized stop-smoking or relapse-prevention program by a staff psychologist.

A major goal was to decrease LDL-C to <2.84 mmol/L (110 mg/dL), to decrease Tg concentrations to <1.13 mmol/L (100 mg/dL), and to increase HDL-C concentrations to >1.42 mmol/L (55 mg/dL). If the SCRIP staff concluded that it was unlikely that a risk-reduction subject would meet the maximal LDL-C goals within the first year without drug therapy, a cholesterol-lowering drug regimen was added. A drug sequence similar to that now recommended by the National Cholesterol Education Program (NCEP) was followed, starting with a bile acid-binding resin (colestipol) and, depending on subject response, adding or substituting other drugs including niacin, gemfibrozil, lovastatin (available only during last half of the study), and probucol. SCRIP differed from the NCEP approach to LDL-C reduction by setting an LDL-C target at 2.84 mmol/L (110 mg/dL) instead of 3.36 mmol/L (130 mg/dL), by using more aggressive guidelines for fat and cholesterol intake, and by using triple-drug therapy when necessary. All lipid medications were provided to the risk-reduction subjects free of charge.

The risk-reduction subjects were provided verbal and written goals and instructions for their individualized risk-reduction plan. To track their progress, contact was maintained with the SCRIP staff using telephone and mail. Risk-reduction subjects returned every 2 or 3 months to the clinic to have their progress evaluated and receive additional assistance. During

these visits, lipids, body weight, and blood pressure were measured; diet, exercise, and smoking program assistance was provided; and hypolipidemic drug therapy was evaluated and revised as needed.

### Statistical Analysis

Comparison of group differences in baseline demographic, clinical, risk factor, and angiographic status was performed with two-sample *t* tests for continuous variables and  $\chi^2$  tests for categorical variables. These same statistics were used to compare baseline characteristics of subjects who completed the study with those of subjects who failed to complete the study for any reason. The effect of the risk-reduction program on selected risk factors was evaluated by calculating on-study risk factor values for each subject, and these values were used to calculate a group on-study average. This on-study value was the average of the values obtained for subjects from the annual evaluations performed between baseline and their follow-up arteriogram, usually 4 years. If a subject was missing data from an annual evaluation, an interpolation procedure was used to assign missing values. The significance of the mean change in continuous variable risk factors from baseline to on-study within the groups was determined by one-sample *t* tests and between the groups by two-sample *t* tests. For dichotomous variables such as drug use, the significance within the groups was determined by Fisher's exact test. Between the groups, significance was found by comparing the odds ratios (odds of event at baseline relative to odds at follow-up) for usual-care and risk-reduction groups, using large sample variance formulas.<sup>34</sup>

The primary angiographic end point was the change in the minimal artery diameter for coronary artery segments that exhibited visible atherosclerosis (diseased segments) at baseline. The minimal diameter for each diseased segment was measured on the baseline and follow-up arteriograms, and the baseline value was subtracted from the value for the follow-up arteriogram to obtain the change in minimal diameter. This change (in millimeters) was divided by the actual interval between arteriograms and computed as a change in minimal diameter per year for each segment. Secondary angiographic end points included change in mean diameter of diseased segments, minimal and mean diameters of nondiseased segments, and percent stenosis of diseased segments. The response variable for each of these measurements was the annual rate of change from baseline to follow-up arteriogram calculated using the procedure described for the change in minimal diameter of diseased segments.

For analysis by patient, the average rate of change for each patient was computed from all eligible diseased segments. The within-group change in the minimal diameter of diseased segments was evaluated by a one-sample paired *t* test, and between-group differences were evaluated by a two-sample *t* test. The power of the study was estimated on a "by-patient analysis" as 0.80 to detect a 57% reduction in the rate of narrowing in the minimal diameter of diseased segments in the risk-reduction group versus the usual-care group at  $P=.05$  (two-tailed) if 260 subjects completed the study and provided technically adequate arteriographic data. For analysis by segment, ANOVA was used with segments nested within subjects and subjects nested within groups.

Subsets of patients were classified on the basis of whether the minimal diameter of diseased segments changed by more than a quantitative threshold. This type of analysis permits categorization of patients as "progressing" if any diseased segment exhibits minimal diameter narrowing exceeding the threshold without segment improvement, ie, enlarging by more than the threshold. Patient "regression" is diseased segment improvement without segment worsening; "mixed change" is a combination of worsening and improving segments; and "no change" is absence of either worsening or improving segments. Group differences in the proportion of patients classified in these categories were tested by  $\chi^2$ . We evaluated progression

and regression using the thresholds of 0.2 and 0.4 mm. The threshold of 0.2 mm was based on a threefold multiple of our within-procedure measurement variability (SD, 0.033 mm)<sup>35</sup> and further multiplying by a factor of 2 to account for between-procedures variation.<sup>36</sup> The threshold of 0.4 mm is suggested by Reiber and colleagues<sup>37</sup> based on their analysis of interprocedure variability using the CAAS quantitation system. The use of thresholds is inherently arbitrary and is not considered a primary study end point. However, it provides a basis for categorizing subjects in a manner that is clinically more comprehensible than raw quantitative angiographic data and has been used in other major angiographic trials.<sup>5-9,13-15</sup>

The relations between the change in minimal diameter of disease segments and selected patient characteristics at baseline and on-study and the change from baseline to on-study were determined using univariate regression analysis. Selected variables that were significantly associated ( $P\leq.05$ ) with the change in artery diameter were included in an all-subsets multivariate regression analysis using Mallows Cp criterion.<sup>38</sup>

The number of patients in the two groups who had various clinical events during the 4 years of the study were compared by a Fisher's exact test.<sup>39</sup> A clinical event other than death was considered if it was the event initiating hospitalization; periprocedure events were not included. The rates contributing to rate ratios in Table 7 are found by dividing number of events by number of patient-years for the particular time period. Delta method estimates of the standard errors of rate ratios were used to obtain *P* values and confidence intervals via large-sample Gaussian theory.<sup>40</sup>

The level of significance was set at  $P<.05$  (two-tailed). The SAS statistical package was used for all analyses.

## Results

### Baseline Characteristics and Dropouts

Of the 300 subjects randomized, 274 (91.3%) had follow-up arteriograms performed and were available for analyses. Reasons for loss to follow-up were death (usual care, 3; risk reduction, 3), illness contraindicating angiography (usual care, 4), subject refusal of follow-up arteriogram (usual care, 7; risk reduction, 2), and subject withdrawal from the study before follow-up arteriography (usual care, 4; risk reduction, 3). Of the 274 arteriograms, 28 could not be analyzed for the following reasons: all diseased segments on the baseline arteriogram were eliminated from analysis because of revascularization procedures after randomization (usual care, 1; risk reduction, 2), inadequate film quality (usual care, 6; risk reduction, 8), and failure of a consistent nitroglycerin protocol to be followed for both arteriograms (usual care, 3; risk reduction, 8). Thus, most analyses presented include 127 (82%) of the 155 usual-care subjects and 119 (82%) of the 145 risk-reduction subjects randomized.

Comparisons are presented in Table 3 of selected variables at baseline for usual-care and risk-reduction subjects with complete angiographic data versus subjects who dropped out or were excluded from the analyses. Significant differences between the usual-care and risk-reduction groups include body weight and HDL-C, because the usual-care group had 7.9% women and the risk-reduction group had 16.8% women ( $P=.03$ ) and the usual-care group had a higher dietary intake of cholesterol and a lower ratio of polyunsaturated-to-saturated fat. In the comparison of subjects who contributed angiographic end point results versus those who did not, only baseline diastolic blood pressure and treadmill exercise test performance were significantly lower in patients without angiographic results. Making

**TABLE 3. Characteristics at Baseline of Subjects in Usual-Care and Risk-Reduction Groups With Follow-up Angiographic Measurements Versus Patients Without Comparative Angiographic Results**

Variable	With Comparative Angiographic Results			Without Angiographic Results	
	Usual Care	Risk Reduction	P*	Combined	P†
Percent of total sample (n=300)	127 (42.3%)	119 (39.7%)		54 (18%)	
Age, y	56.2±8.2	58.3±9.2		57.6±9.5	
Male, %	92.1	83.2	.03	79.6	
Occupational status, %					
Professional/white collar	54.4	52.1		57.4	
Blue collar/homemaker	15.6	20.2		20.4	
Retired/unemployed	30.0	27.7		22.2	
Clinical features, %					
History of prior MI	49.6	40.3		54.7	
History of hypertension	42.5	47.1		39.6	
History of diabetes	12.6	10.9		7.6	
Chest pain past 12 mo	71.7	72.3		79.3	
Angiographic features					
Ejection fraction, %	57±12	60±11		56±10	
Vessels >50% stenosis, % patients					
None	6.3	5.9		5.6	
One	36.2	42.0		24.1	
Two	37.0	37.8		48.1	
Three	20.5	14.3		22.2	
SCRIP eligible segments, n per patient					
Diseased	3.2±1.86	3.3±1.82		2.8±1.61	
Nondiseased	6.8±3.28	6.9±3.72		6.0±3.73	
Smoking status					
Current smoker, %	17.3	10.1		14.8	
Ex-smoker, %	56.7	55.5		66.7	
Never smoke, %	26	34.5		18.5	
Cigarettes/d for smokers	21.5±16.9	27.2±10.3		23.0±19.4	
Body composition measures					
Weight, kg	84.7±14.5	80.4±12.7	.02	79.9±16	
Body mass index, kg/m <sup>2</sup>	27.1±3.6	26.8±3.4		26.9±4.2	
Blood pressure, mm Hg					
Systolic	118.1±14.6	121±16.5		117.2±14.8	
Diastolic	72.0±8.5	70.9±9.2		68.8±9.3	.05
Graded exercise test					
Maximum METS	9.1±2.9	8.7±3.4		7.7±3.5	.02
Angina on treadmill test, %	22.4	24.4		26.4	
Dietary assessments					
Calories/kg body wt/d	25.0±8.4	24.2±7.4		23.0±7.7	
Calories from fat, %	32.6±7.8	31.5±8.6		30.9±8.7	
P:S ratio	0.82±0.43	0.95±0.49	.03	0.85±0.41	
Cholesterol intake, mg/d	284±149	237±126	.008	244±140	
Lipid profile, mmol/L					
Triglycerides	1.75±1.41	1.77±1.22		1.67±0.93	
Total cholesterol	5.87±0.96	6.03±1.05		5.97±0.96	
LDL cholesterol	4.03±0.87	4.09±0.92		4.14±1.06	
HDL cholesterol	1.10±0.28	1.19±0.32	.03	1.08±0.28	
Glucose tolerance test (n for fasting, 125, 119, 152; n for nonfasting, 116, 106, 48, mmol/L)					
Fasting glucose	5.74±2.02	5.78±1.35		5.62±1.24	
1-Hr postload glucose	8.92±3.18	8.62±3.18		8.53±3.18	
Revised Framingham risk score	14.9±10.7	16.5±12.1		14.2±9.3	

MI indicates myocardial infarction; METS, multiple of resting energy expenditure; P:S, polyunsaturated:saturated fat in diet; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.

\*For comparison of the usual-care versus the risk-reduction subjects.

†For comparison of all subjects with comparative angiographic measurements with subjects without these measurements. All  $P < .05$  values are listed.

**TABLE 4. Comparison of the On-Study Intervention in Usual-Care Versus Risk-Reduction Groups for Patients With Comparative Angiographic Measurements**

Variable	Usual Care			Risk Reduction			P*
	Baseline	On-Study	Absolute Change	Baseline	On-Study	Absolute Change	
Exercise intervention (n=126, 118)							
Participation in exercise training program on a regular basis, %	72±45	70±34	-2.0	79±41	90±23	21	.02
Participation in routine (daily) activities promoted by risk-reduction program (average number of routine activities participated in by each subject)	1.83±1.31	1.95±1.07	0.14	1.74±1.30	2.20±0.92	0.46‡	.02
Dietary intervention (n=126, 118)							
Calories from fat, %	32.6±7.8	32.7±7.2	+0.1±6.7	31.5±8.6	23.8±7.0	-7.7±7.6¶	.0001
Calories from saturated fat, %	10.3±3.4	10.6±3.3	+0.3±2.8	9.8±4.0	6.8±2.8	-2.9±3.0¶	.0001
P:S ratio	0.81±0.43	0.79±0.34	-0.03±0.40	0.94±0.49	1.05±0.38	+0.1±0.4§	.01
Cholesterol intake, mg/d	284.2±149.3	270.7±135.5	-13.5±104	237.4±126.3	143.4±74.3	-94.1±115.1	.0001
Hypolipidemic drug intervention (n=127, 119)							
Any hypolipidemic drug							
At any time during study, %	6.3	30.7	24.4	12.6	93.3	80.7	<.0001
Total on-study months, 48 max	NA	8.1±14.8		NA	36.0±13.9		
Specific on-study drug use (4th year)‡							
Bile acid-binding resin, %	2.4	10.2	7.9	8.4	68.1	59.7	.0002
Niacin, %	2.4	11.8	9.4	1.6	37.8	36.1	.006
Fibric acid compounds, %	3.1	3.90	0.8	3.4	20.2	16.8	.025
HMG CoA reductase inhibitors, %	0	9.4	9.4	0	36.1	36.1	.046
Probucol, %	0	0	0	0	4.2	4.2	.088
Other concurrent medications (4th year)† (n=127, 119)							
β-Blocking drugs, %	40.9	26.0	-15.0	37.0	26.1	-10.9	.433
Calcium antagonists, %	59.1	40.9	-18.7	61.3	44.5	-16.8	.480
Diuretics, %	15.7	13.4	-2.4	13.4	10.9	-2.5	.483
Nondiuretic, non-β, noncalcium blocker							
Antihypertensives, %	5.5	14.2	8.7	5.0	11.8	6.7	.452
Hypoglycemics, %	5.5	7.9	2.4	7.6	8.4	0.8	.403
Antiplatelet, aspirin, %	72.4	75.6	3.2	67.2	75.6	8.4	.405

\*P represents the comparison of usual-care versus risk-reduction group for the change from baseline to on-study values.

†Some patients were taking more than one medication.

‡P<.05, §P<.01, ||P<.001, ¶P<.0001, within-group comparison for the change in baseline and on-study values.

allowance for the multiplicity of comparisons, there is little evidence for overall bias induced by failure of randomization or by biased selection of patients for follow-up.

### Risk-Reduction Program Participation

Subjects in the risk-reduction group were instructed at clinic visits in all relevant components of the multifactor risk-reduction program. The risk-reduction subjects averaged 23.1±7.9 clinic visits during the 4 years with an average of 7.0, 6.2, 5.3, and 4.6 visits in years 1 through 4,

respectively. Participation in risk-reduction activities for subjects in the usual-care and risk-reduction groups during the on-study period is summarized in Table 4. Reported physical activity was high at baseline in both groups and increased on-study in the risk-reduction group to a greater extent than in usual-care subjects. Risk-reduction subjects achieved large reductions in total fat, saturated fat, and cholesterol intake, whereas there were no significant changes in the usual-care group.

At baseline, 6.3% of the usual-care and 12.6% of the risk-reduction subjects were taking lipid medications

**TABLE 5. Comparison of On-Study Risk Factor Measurements in Usual-Care and Risk-Reduction Groups for Patients With Comparative Angiographic Measurements**

Variable	Usual Care (n=127)			Risk Reduction (n=118)			P*
	Baseline	On-Study	Absolute Change	Baseline	On-Study	Absolute Change	
<b>Cigarette smoking</b>							
Current smokers, %	17.3 (n=22)	18.1 (n=23)	+0.8	10.1 (n=12)	10.1 (n=12)	0.0	.47
<b>Body composition</b>							
Weight, kg	84.6±14.5	85.5±15.0	+0.9±3.6§	80.4±12.7	77.4±11.9	-3.0±4.0¶	.0001
Body mass index, kg/m <sup>2</sup>	27.1±3.6	27.4±3.9	+0.3±1.2§	26.8±3.4	25.8±3.3	-1.0±1.3	.0001
Sum of skinfolds, mm	52.7±17.1	53.2±16.4	+0.5±13.1	52.8±17.9	46.4±14.7	-6.4±13.6	.0001
<b>Blood pressure, mm Hg</b>							
Systolic	118.1±14.7	121.2±13.3	+3.1±10.5¶	121.1±16.5	120.5±14.1	-0.6±11.1	.008
Diastolic	72.0±8.0	72.4±7.6	+0.4±6.6	70.9±9.2	69.6±7.9	-1.3±7.1‡	.066
<b>Graded exercise test</b>							
Maximum MET level	9.1±2.9	9.9±3.0	+0.7±2.1¶	8.6±3.4	10.3±3.5	+1.7±2.4¶	.001
Heart rate at 4 METS, bpm	98.6±16.6	94.4±12.9	-4.2±11.5¶	101.6±18.6	96.1±14.9	-5.5±15.0¶	.680
<b>Lipoprotein profile</b>							
Total cholesterol, mmol/L	5.87±0.96	5.79±0.75	-0.09±0.63	6.03±1.05	5.03±0.73	-0.99±0.83¶	.0001
LDL cholesterol, mmol/L	4.04±0.87	3.89±0.67	-0.16±0.59	4.07±0.93	3.12±0.60	-0.95±0.81¶	.0001
HDL cholesterol, mmol/L	1.10±0.28	1.16±0.29	0.06±0.17¶	1.19±1.49	1.33±0.38	0.14±0.23¶	.001
Total/HDL cholesterol	5.60±1.46	5.28±1.31	-0.32±0.98	5.36±1.49	4.08±1.15	-1.27±1.04¶	.0001
Triglycerides, mmol/L	1.75±1.41	1.76±0.91	0.01±0.97	1.77±1.22	1.42±0.69	-0.34±0.87¶	.002
Lp(a), mg/dL (n=98, 97)†	19.8±21.4	19.9±25.4	0.14±12.1	19.2±27.3	18.1±27.8	-1.06±13.4	.51
Apolipoprotein B, mg/dL (n=99, 97)†	112.2±32.1	105.1±38.6	-7.0±43.0	116.5±35.1	90.3±33.5	-26.2±34.8¶	.0008
<b>Glucose tolerance test (n for fasting, 125, 116; n for nonfasting, 112, 104)</b>							
Fasting glucose, mmol/L	5.79±2.02	6.16±1.80	0.37±1.73‡	5.79±1.36	5.62±1.36	-0.17±1.15	.005
1-Hr postload glucose, mmol/L	8.82±3.18	9.03±3.63	0.20±2.71	8.66±3.21	7.64±2.67	-1.03±2.38¶	.0005
Fasting insulin, pmol/L	123±83	126±91	3±85	130±191	101±87	-30±133‡	.033
1-Hr postload insulin, pmol/L	947±579	959±745	11±641	916±570	823±749	-93±667	.084
<b>Revised Framingham coronary heart disease risk score</b>	15±7	14±6	-0.5±3	15±7	11±0.06	-4.0±0.04¶	.0001

MET indicates multiple of resting energy expenditure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; and Lp(a), lipoprotein(a).

\*P represents the comparison of usual-care versus risk-reduction group for the change from baseline to on-study values.

†For Lp(a) and apolipoprotein B, on-study sample measured only at year 4.

‡P<.05, §P<.01, ¶P<.001, ¶¶P<.0001, within-group comparison for the change from baseline to on-study values.

(Table 4). At 1 year, 11.0% of the usual-care subjects were prescribed lipid medications by their personal physician; in contrast, 70.6% of the risk-reduction subjects were placed on lipid medications by SCRIP staff. At the 4-year follow-up, these percentages rose to 22.6% of usual-care subjects versus 89.9% of risk-reduction subjects. During the study, 75.6% of subjects in each group were taking antiplatelet drugs, including aspirin (Table 4). Antianginal and antihypertensive drugs were used equally in both groups at baseline and on-study, with similar reductions in the use of  $\beta$ -blockers and calcium antagonists on-study in both groups.

#### Risk Factor Changes in Usual-Care and Risk-Reduction Groups

Substantial favorable changes in risk factor status occurred for patients in the risk-reduction group from baseline to on-study compared with the usual-care

group. Significant differences were achieved in body composition, blood pressure, exercise test performance, plasma lipoprotein concentrations, glucose and insulin, and a composite risk score (Table 5). For example, on-study LDL-C and apo B were reduced by 22%, Tg was reduced by 20%, HDL-C was increased by 12%, and the Framingham risk score was decreased by 22%.<sup>41</sup> Mean Lp(a) values [and log Lp(a)] did not change significantly from baseline to year 4 in either group. Among smokers, the reported number of cigarettes smoked per day decreased by 12.1 per day in risk-reduction subjects, not significantly different from usual-care subjects. Risk factor changes in the usual-care group were small with several showing significant improvement and others becoming significantly worse. Risk factor changes were similar in men and women (data not shown), but because of the small sample size for women (usual care, 20; risk reduction, 10), group

TABLE 6. Comparison of Baseline and Changes in Angiographic Measurements

	Baseline			Absolute Change per Year		
	Usual Care	Risk Reduction	P†*	Usual Care	Risk Reduction	P‡†
Analysis by patient						
Visibly diseased segments	n=127	n=119				
Minimal diameter, mm*‡	2.426±0.569	2.271±0.493	.02	-0.045±0.073	-0.024±0.067	.02
Mean diameter, mm	3.073±0.592	2.909±0.542	.02	-0.037±0.074	-0.022±0.046	.06
Stenosis, %	29.7±8.3	30.7±6.5	.28	0.7±2.0	0.5±2.1	.50
Visibly nondiseased segments	n=131	n=126				
Minimal diameter, mm	2.364±0.456	2.341±0.484	.20	-0.024±0.052	-0.020±0.048	.48
Mean diameter, mm	2.742±0.475	2.703±0.486	.51	-0.016±0.051	-0.015±0.048	.94
Nested analysis by segment						
Visibly diseased segments	n=391	n=379				
Minimal diameter, mm	2.344±0.739	2.226±0.663	.02	-0.051±0.125	-0.021±0.078	.0003
Mean diameter, mm	2.993±0.796	2.859±0.724	.02	-0.042±0.137	-0.022±0.070	.02
Stenosis, %	30.5±11.1	30.9±10.0	.60	0.9±3.5	0.3±2.5	.02
Visibly nondiseased segments	n=832	n=815				
Minimal diameter, mm	2.346±0.788	2.308±0.815	.33	-0.016±0.088	-0.019±0.079	.23
Mean diameter, mm	2.716±0.808	2.666±0.837	.22	-0.018±0.078	-0.015±0.073	.62

Follow-up duration: usual care, 3.96 years; risk reduction, 4.02 years ( $P=.20$ ).

Values are mean±SD.

\*Level of significance for comparison of baseline values between two groups.

†Level of significance for comparison of absolute change per year between two groups.

‡Minimum diameter of visibly diseased segments is primary angiographic study end point.

differences in these changes were not significant. There were no significant relations between subject age and magnitude of risk factor change in either group.

### Angiographic Changes

#### Primary Angiographic End Point: Change in Minimal Diameter of Visibly Diseased Segments

Baseline and follow-up arteriography with good-quality visualization of diseased segments was available for 127 usual-care and 119 risk-reduction subjects with an average follow-up interval of  $3.96\pm0.43$  years for usual-care and  $4.03\pm0.27$  years for risk-reduction subjects. A total of 17 subjects (usual care, 11; risk reduction, 6) had clinically indicated arteriograms between 1 and 3.75 years and no protocol-mandated arteriogram at 4 years. At baseline, the average minimal and average mean diameters for visibly diseased segments were significantly larger in the usual-care than the risk-reduction group (Table 6). These differences in the baseline minimal diameter between groups were mainly the result of differences in the female patients (women usual care, 2.51 mm; risk reduction, 2.07 mm;  $P=.01$ ; men usual care, 2.42 mm; risk reduction, 2.31 mm;  $P=.15$ ).

Both groups demonstrated net progression of disease defined by the change in minimal diameter of visibly diseased segments (Table 6). The rate of change in minimal diameter per patient in the risk-reduction group was 47% less than for the usual-care group ( $P=.02$ ). The difference in the rate of change in minimal diameter of diseased segments between usual-care and risk-reduction groups remained significant when adjusted for age and baseline segment diameter ( $P=.03$ ). Also, the comparison of the changes in minimal diameter of visibly diseased segments was adjusted for those

variables with mean baseline values that were different for the usual-care and risk-reduction groups by  $P<.15$ . This analysis of covariance included age, sex, dietary cholesterol, ratio of polyunsaturated to saturated fat, smoking status, body weight, HDL-C, and minimal artery diameter and produced a group effect of 0.020 mm/y difference between the two groups ( $P=.04$ ). Also, when adjusted for baseline age, sex, number of patients with three-vessel disease, ejection fraction, and minimal diameter of diseased segments, the difference in the change in minimal diameter of diseased segments between the two groups remained at 0.02 mm/y. Thus, it appears that baseline differences between the two groups do not account for the differences in the rate of disease progression during treatment. When segments instead of subjects were used as the unit of analysis with adjustment for within-patient correlation of segment responses, the decrease in minimal diameter in the risk-reduction group was 58% less than for the usual-care group ( $P=.0003$ ).

Differences in rates of change in minimal diameter between the usual-care and risk-reduction groups were somewhat greater for women than for men. When analyzed by patient, the annual rate of change for men in the usual-care group ( $n=117$ ) was  $-0.045$  mm/y versus  $-0.026$  mm/y for the risk-reduction group ( $n=99$ ) ( $P=.06$ ). In women, the change was  $-0.046$  mm/y for the usual-care group ( $n=20$ ) versus  $-0.016$  mm/y for the risk-reduction group ( $n=10$ ) ( $P=.27$ ). Nested segment analysis yielded similar results but they were statistically significant (men: usual care,  $-0.051$  mm/y; risk reduction,  $-0.023$  mm/y;  $P=.002$ ; women: usual care,  $-0.055$  mm/y; risk reduction,  $-0.011$  mm/y;  $P=.02$ ). The number of segments analyzed was 364 in usual-care men and 316 in risk-reduction men

and 27 in usual-care women and 63 in risk-reduction women.

### Secondary Angiographic End Points

Secondary analyses included mean diameter and percent stenosis of visibly diseased segments and minimal and mean diameters of segments that were not visibly diseased at baseline (Table 6). The rate of change by subject in mean diameter of diseased segments was 41% less in the risk-reduction group than in the usual-care group ( $P=.06$ ). The difference in the rate of change in percent stenosis between groups was 29% ( $P=.50$ ). Rates of change in both minimal and mean diameters of nondiseased segments were substantially less than the corresponding rates of change in diseased segments in both groups. This difference in the rate of change between diseased and nondiseased segments was especially evident in the usual-care group where the rate of change by subject in mean diameter of nondiseased segments was 57% less than that of diseased segments. The differences in the rate of change in nondiseased segments between the two groups were not significant by patient or by segment.

The distribution of patients between the usual-care and risk-reduction groups into mutually exclusive categories based on segment change exceeding thresholds of 0.2 and 0.4 mm (see "Methods") was significant at  $P=.07$  and  $P=.001$  levels, respectively (Fisher's exact test, two-tailed; similar results were obtained when the data were analyzed using a  $2 \times 3$  table;  $P=.07$  and  $P=.002$ , respectively). For a threshold of 0.2 mm, there were 10.3% of usual-care versus 20.2% of risk-reduction patients in the regression category and nearly equal numbers of patients in both groups in the progression category (usual care, 49.6%; risk reduction, 50.4%). The patients with no change represented 19.7% of the usual-care group and 17.6% of the risk-reduction group. The mixed-change patients represented 20.5% of the usual-care patients and 11.8% of the risk-reduction patients. When the data were analyzed by segment, the percentage of segments demonstrating regression (usual care, 12.5%; risk reduction, 14%), no change (usual care, 46.0%; risk reduction, 56.7%), or progression (usual care, 41.4%; risk reduction, 29.3%) was significantly different for the two groups ( $P=.002$ ). Similar results were observed using a 0.4-mm threshold, although substantially fewer segments met the criteria for progression or regression.

### Multivariate Analyses

Univariate and multivariate regression analyses were performed to determine if specific patient characteristics measured at baseline or on-study or calculated as a change from baseline to on-study were predictive of the primary outcome—rate of change in minimal diameter of diseased segments. The major variables listed in Tables 3 through 5 were included in these analyses. For all subjects ( $n=228$ ), the best two-variable model was change in treadmill exercise test performance (max METS) and change in Framingham risk score (consisting of changes in systolic blood pressure, ratio of TC to HDL-C, and cigarette smoking status), with an increase in treadmill exercise performance and a decrease in risk score related to a reduced rate of progression ( $P=.002$ ,  $R^2=.05$ ). The best three-variable model included change in max METS, change in Framingham risk score, and

percent of energy from fat at baseline ( $P=.002$ ,  $R^2=.07$ ), with a higher percentage of fat associated with a greater rate of progression.

### Clinical Events

#### Cardiac Events

On-study clinical cardiac events are summarized in Table 7. During the study, 6 patients died (usual care, 3; risk reduction, 3), with three cardiac or sudden unexplained deaths in the usual-care group and two cardiac or sudden unexplained deaths and one death from cancer in the risk-reduction group. During 4 years, the number of patients with nonfatal myocardial infarctions and cardiac-related death was not significantly different between groups (usual care, 11; risk reduction, 6;  $P=.23$ ), but the difference in the number of cardiac deaths and hospitalizations for nonfatal myocardial infarction, PTCA (primary procedures only), and CABG (usual care, 44; risk reduction, 25) was significant ( $P=.05$ ). The total number of patients with a primary cardiac event over the 4 years in the usual-care group was 35 and in the risk-reduction group was 20 ( $P=.07$ ). Most clinical cardiac events in the risk-reduction group occurred during the first year that patients were enrolled in the study (17, or 68% of all events in risk-reduction group during 4 years) compared with only 9 events in the usual-care group during the first year (20% of all events in usual-care group during 4 years) ( $P=.09$ ). During the next 3 years, risk-reduction patients were hospitalized for clinical cardiac events only 8 times compared with 35 times for the usual-care patients (rate ratio, 0.24; 95% confidence interval, 0.13 to 0.47;  $P=.0003$ ). Repeat PTCA for the same lesion was performed in 14 usual-care patients (15 procedures) and in 18 risk-reduction patients (21 procedures) ( $P=.13$ ).

#### Noncardiac Clinical Events

During the on-study period, a total of 28 usual-care patients were hospitalized for noncardiac reasons, as were 37 patients in the risk-reduction group ( $P=.13$ ). Major reasons (nonexclusive) for these hospitalizations included atherosclerotic vascular disease (usual care, 16; risk reduction, 12), gastrointestinal (usual care, 5; risk reduction, 10), orthopedic (usual care, 4; risk reduction, 7), cancer (usual care, 7; risk reduction, 2), and general surgery (usual care, 4; risk reduction, 7). No cause-specific reason for hospitalization was significantly different between the two groups. In the risk-reduction group, gastrointestinal reasons for hospitalizations included pancreatitis (3), cholecystectomy (2), hepatitis (2), diverticulitis (1) diverticulosis (1), and gastrointestinal bleed (1). One hospitalization was considered possibly related to the risk-reduction program; a patient taking 1 g niacin TID was hospitalized for hepatitis.

#### Adverse Events

The adverse event experience in the risk-reduction group was generally favorable with no patient requiring any type of medical care as a result of participation in the exercise program. A check of serum nutrient levels of selected patients indicated that the diet did not produce any nutritional deficiencies (data not presented). Results from the 4-day food records demonstrated no adverse changes in vitamin or mineral intake and in some instances resulted in a beneficial change (eg,

**TABLE 7. Major Clinical Cardiac Events During Study for All Randomized Patients**

	Follow-up Year				Total Events
	1	2	3	4	
<b>Cardiac or sudden unexplained death</b>					
Usual care	0	2	0	1	3
Risk reduction	1	0	0	1	2
<b>Nonfatal MI</b>					
Usual care	0	1	3	6‡	10
Risk reduction	4	0	0	0	4
<b>CABG</b>					
Usual care	6	4	4	0	14
Risk reduction	3	2	1	0	6
<b>Primary PTCA*</b>					
Usual care	3	3	7	4	17
Risk reduction	9	2	1	1	13
<b>Total no. of cardiac events initiating hospitalization (deaths, MI, CABG, and primary PTCA)†</b>					
Usual care	9	10	14	11	44
Risk reduction	17	4	2	2	25
Rate ratio	2.03	0.43	0.15	0.19	0.61
Significance ( <i>P</i> )	0.09	0.15	0.01	0.03	0.05
95% Confidence interval	1.0-4.0	0.2-1.1	0.04-0.5	0.06-0.7	0.4-0.9
<b>Total no. of patients having primary cardiac events</b>					
Usual care	9	10	12	10	34§
Risk reduction	16	4	2	2	20
Odds ratio	2.01	0.41	0.17	0.20	0.57
Significance ( <i>P</i> )	0.14	0.17	0.01	0.03	0.07
95% Confidence interval	0.9-4.7	0.1-1.4	0.4-0.8	0.4-0.9	0.3-1.0

MI indicates myocardial infarction; CABG, coronary artery bypass graft surgery; and PTCA, percutaneous transluminal coronary angioplasty.

Listed in table are number of primary cardiac events initiating hospitalization.†

\*Defined as primary PTCA and excludes post-MI PTCA and restenosis (within 6 months of primary PTCA).

†Only the initial cardiac event that occurred during hospitalization is included. No MI, PTCA, or CABG occurred without hospitalization.

‡Two of these patients had MIs previously.

§Nine usual-care patients had multiple separate hospitalizations.

||Three risk-reduction patients had multiple separate hospitalizations.

significant increases in vitamin C, beta-carotene, and dietary fiber intake). Adverse events resulting from lipid medication use in the risk-reduction group were usually managed by reducing the dose of the offending drug or, less frequently, by switching to another drug. Over the 4 years, a total of 37 subjects were taken off a lipid medication because of adverse reactions: abnormal liver function tests (3), skin rash (9), constipation (9), and nausea (20) (4 subjects had multiple reactions).

### Discussion

The combination of lifestyle changes and use of lipid-altering medications individualized to meet each patient's needs resulted in a highly significant improvement in the overall risk profile of the risk-reduction patients compared with the small changes in risk status of patients assigned to the usual care of their physician. This risk factor reduction significantly decreased angio-

graphically defined progression of coronary atherosclerosis as well as hospitalizations for clinical cardiac events. Significant changes were obtained in lipid and lipoprotein levels, glucose and insulin levels, adiposity, exercise test performance, dietary intake of fat and cholesterol, and measures of physical activity. We were not successful in reducing the smoking rate among the small group of smokers. The risk-reduction program was comprehensive, promoted substantial changes, and was sustained by patients attending the clinic approximately once every 2 to 3 months over 4 years. Also noteworthy was the very limited improvement in most risk factors in the usual-care patients considering that all patients had known coronary disease and the results of their annual evaluations were returned to them and their personal physicians. Nearly all participants had personal primary care physicians, consulting cardiologists, and health insurance. At baseline, both groups reported diets that

were close to the NCEP Step 1 diet<sup>42</sup> and had blood pressures that were well controlled.

### SCRIP Results Compared With Other Angiographic Trials

During the past decade, a number of randomized clinical trials using arteriography have reported the effect of various interventions on the rate of progression of coronary atherosclerosis in humans.<sup>4-11,13-15</sup> These studies were primarily single-factor interventions involving lipid-lowering medications and/or diet,<sup>4-8,15</sup> ileal bypass surgery,<sup>9</sup> or the use of calcium channel antagonists.<sup>10,11</sup> The results of two other multifactor trials have been reported.<sup>13,14</sup> Subjects have included mainly men with established coronary artery disease<sup>5,6,9-11</sup> and/or substantial hyperlipidemia,<sup>7,8,15</sup> except for the study by Kane and colleagues,<sup>8</sup> which included women as well as men with familial hypercholesterolemia. In all of these studies, all of the subjects demonstrated some degree of atherosclerosis by coronary arteriography. Studies showing large reductions in LDL-C with<sup>5-7</sup> or without<sup>8,9,13,15</sup> large increases in HDL-C reported significantly less progression of disease in the treatment groups. These studies use various angiographic measurement procedures, making it difficult to compare angiographic results among trials. Qualitative comparisons of the major angiographic end points in the seven studies that focused primarily on lipid lowering and used quantitative arteriographic procedures reveal that the rate of progression is reduced by approximately 50% in three studies (References 5 and 9 and SCRIP), whereas in four studies,<sup>7,8,13,15</sup> treatment groups showed net regression of disease and the control groups showed net progression. In general, it appears that better angiographic outcomes are achieved with greater reductions in LDL-C because studies reporting regression of disease in their treatment groups produced reductions in LDL-C of 35% or more.<sup>7,8,13,15</sup> However, the diet-only group in STARS<sup>15</sup> demonstrated net regression but had a reduction in LDL-C of only 16% (and no change in HDL-C), and in CLAS,<sup>5</sup> a mean reduction in LDL-C of 43% did not produce net regression. An increase in HDL-C does not appear essential to achieve regression because two<sup>7,8</sup> of the four studies demonstrating net regression in their treatment groups achieved significant increases in HDL-C, but the other two studies<sup>13,15</sup> did not.

The angiographically based studies just cited consistently obtained more favorable results than the recently reported major primary prevention trials using nonfatal myocardial infarction and cardiac death as primary outcomes.<sup>1,2,12,42</sup> The Lipid Research Clinics' Primary Prevention Trial<sup>1</sup> and the Helsinki Heart Study<sup>2</sup> resulted in significant reductions in clinical cardiac events, but no such benefits were reported for the Multiple Risk Factor Intervention Trial,<sup>12</sup> and the Helsinki Multifactor Primary Prevention Trial<sup>42</sup> had no benefit and possibly had some increased risk for selected subjects in the treatment group. It is not possible to directly compare the efficacy of these angiographic and clinical outcome studies because of numerous differences in study design besides the primary outcome variables, including subject selection and nature of the intervention programs. In the angiographic studies, all of the subjects had some degree of coronary atherosclerosis and thus are generally considered to be secondary prevention studies, whereas the clinical outcome studies

are considered primary prevention trials even though it is likely that some of the subjects, because they were selected for their high-risk profile, had coronary atherosclerosis as defined by coronary angiography. Also, most of the angiographic trials with positive results used more intensive intervention programs, including multiple lipid drug therapy, lifestyle plus lipid drugs, or more extensive dietary changes than the clinical outcome studies.

### Additional Information Provided by SCRIP

SCRIP contributes substantial new information on the success of intensive multifactor risk reduction in decreasing the rate of coronary atherosclerosis progression and clinical cardiac events in men and women with CAD but not necessarily with elevated blood lipids. Angiographic benefits occurred even in subjects with a relatively low risk profile. For example, the mean LDL-C for risk-reduction subjects at baseline was 4.09 mmol/L (158 mg/dL), slightly lower than that recommended for drug treatment by NCEP guidelines<sup>43</sup> for patients with established coronary artery disease and generally lower than that in previously reported angiographic trials. Also, the results of the univariate and multivariate regression analyses indicate that the angiographic changes were associated more with the changes in various risk factors than with their baseline values (these data will be reported in detail separately).

Plasma Lp(a) concentrations have a large genetic component<sup>44</sup> and are positively associated with coronary heart disease.<sup>45</sup> Attempts to alter Lp(a) by *N*-acetylcysteine<sup>46,47</sup> and diet<sup>48,49</sup> have not produced consistent changes. Anabolic steroids cause significant reductions in Lp(a),<sup>50</sup> and large doses of niacin significantly reduced Lp(a) in selected patients.<sup>7,51</sup> However, Lp(a) concentrations in SCRIP did not change from baseline to 4 years in either the usual-care or risk-reduction group, nor was the change significant for those risk-reduction subjects who took niacin for 12 months or longer. The change in Lp(a) was  $-1.8 \pm 16.0$  mg/dL for subjects taking niacin ( $n=48$ ) and  $-0.3 \pm 10.4$  mg/dL for subjects not taking niacin ( $n=49$ ;  $P=.60$ ). Baseline values and changes in Lp(a) were not associated with significant change in minimal artery diameter of diseased segments.

Criteria were used in the prospective selection of artery segments for analysis in SCRIP that would enhance our ability to detect a change in the rate of progression of coronary atherosclerosis rather than detect the complicating features of thrombosis or occlusion. Only visibly diseased segments of <70% diameter narrowing at baseline were selected, and any segments that were influenced by coronary instrumentation or bypass graft placement during revascularization procedures were excluded. Complete segment occlusion occurred on-study in lesions that at baseline were <70% narrowed in three patients (usual-care, 2; risk-reduction, 1). Of the 54 patients without comparative arteriograms, there were 3 usual-care and 3 risk-reduction patients who died of cardiac reasons or had a nonfatal myocardial infarction that hypothetically could have represented vessel occlusion.

Diseased segments (<70% narrowed) were expected to demonstrate a more rapid rate of disease progression than nondiseased segments, yet would be less likely to be lost to follow-up because of revascularization procedures during the course of the study than segments with

more advanced disease. Moreover, restricting baseline lesion severity to  $<70\%$  and requirement of a segment diameter of  $>1.5$  mm minimized the problem of diminished precision for measuring diameters of  $<1.0$  mm at follow-up. These criteria eliminated from the primary analyses segments without visible disease at baseline as well as segments with severely stenotic lesions. Thus, the severity of atherosclerosis in SCRIP-eligible segments was less than that generally included in other recently reported angiographic trials. This exclusion of severely diseased segments and the generally low-risk profile of patients at baseline likely account for the relatively slow rate of disease progression in the usual-care group.

When SCRIP angiographic results are analyzed by segment, the decrease in rate of narrowing in minimal diameter of diseased segments for the risk-reduction group was 59% less than that for the usual-care group ( $P=.0003$ ). The total difference between the two groups in the change in artery diameter over 4 years was 0.084 mm. Even though this reduction in rate of progression is small, if it continued over a decade or longer, it would have a highly favorable effect on coronary artery lumen size and coronary reserve.

Differences in cardiac event rates between the two groups were not a primary a priori end point of the study. However, the reduction in both hospitalizations for primary cardiac events in the risk-reduction group ( $P=.05$ ) and the number of patients experiencing cardiac events ( $P=.07$ ) is consistent with favorable effects of the intervention on progression of atherosclerosis. During the first year, the cardiac event rate was somewhat higher in the risk-reduction subjects ( $P=.09$ ), but for the last 3 years, the total of 8 events leading to hospitalization experienced by the risk-reduction subjects was remarkably low compared with 35 events in the usual-care group. In trials of lipid management with clinical events as the primary outcome, the reduced event rate in the treatment group generally did not become evident until the second or third year of treatment.<sup>1-3</sup> The SCRIP data are consistent with this experience. None of the four myocardial infarctions in the risk-reduction subjects during the first year appeared to be related to the treatment program; however, the increased rate of PTCA during the first year in the risk-reduction subjects may have been a result of their more frequent contact with the SCRIP staff.

None of the recent reported angiographic studies were designed to detect the effects of the treatment on the rate of clinical cardiovascular events, but four of them (References 7, 9, and 15 and SCRIP) have reported a significantly lower rate in the treatment compared with the placebo or usual-care group. These studies have involved subjects with angiographically defined coronary artery disease and are considered to be trials of secondary prevention. Why they appear to be somewhat more effective in reducing cardiovascular events than several of the primary prevention studies that have used clinical outcomes as their major end point<sup>1-3,12,42</sup> is not obvious. It could be that secondary prevention is more effective than primary prevention, but the angiographic (secondary prevention) trials included more intensive treatment regimens, resulting in greater differences in risk factor status between the treatment and control groups than in the primary prevention trials.

Intensive risk reduction could decrease clinical cardiac events independent of its effects on coronary atherosclerosis because it might change internal artery diameter by altering vascular tone or thrombotic activity. Stasis, coronary blood flow velocity, circulating promoters of platelet adhesion, fibrinolytic activity, and native vessel size may all independently contribute to thrombosis and could have been affected by one or more of the risk factor interventions in SCRIP. Also, myocardial oxygen demand would be decreased by a reduction in heart rate and blood pressure at rest and during exertion, and decreased smoking could lead to improved oxygen supply to the myocardium. Others have promoted the concept that acute myocardial infarction, sudden cardiac death, or unstable angina can result from the endothelial disruption of hemodynamically nonsignificant lesions, causing rapid narrowing or closure of the artery as a result of platelet aggregation and thrombosis.<sup>52</sup> Such a process might explain the reduction of clinical cardiac events in the treatment groups in the Familial Atherosclerosis Treatment Study,<sup>8</sup> the Program on the Surgical Control of Hyperlipidemias,<sup>53</sup> and SCRIP. It may be that risk-reduction efforts, including dietary modifications, exercise, weight loss, and lipid medication, exert clinical benefits that are not explained solely by a volume reduction in intramural coronary atheroma.

### Implications

SCRIP results support the hypothesis that patients with coronary artery disease who sustain substantial improvement in risk factors decrease the rate of progression of their coronary atherosclerosis and hospitalizations for cardiac events. Further analyses of the SCRIP data may provide more insight into which factors made significant contributions to these favorable results, but other studies are needed to determine the extent to which factors other than lipoprotein management are of value. The success of SCRIP in managing risk factors over 4 years indicates that consideration should be given to including intensive multiple risk factor modification in the treatment of patients with coronary artery disease. SCRIP used a "physician-supervised, nurse case-manager" model with consultation from other health professionals that could be implemented in a variety of health care settings. Subjects in the risk-reduction group attended the clinic approximately every 2 months during the first 2 years and once every 3 months during the last 2 years, and no special facilities were required.

The inhibition of lumen encroachment, albeit small, and particularly the decrement in clinical event rates observed in SCRIP and other recent angiographic-based studies demonstrate the potential for long-term benefits that may be comparable to those achieved by revascularization procedures. For example, PTCA has been somewhat disappointing in maintaining long-term patency of coronary arteries,<sup>54</sup> with a  $\leq 34\%$  requirement for subsequent revascularization procedures over 2 years in multivessel disease.<sup>55</sup> Perhaps future studies using more contemporary and intensive risk factor intervention strategies will provide a better counterpoint for comparison with revascularization strategies.

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