Management of Hypercholesterolemia

Combined Intense Lifestyle and Pharmacologic Lipid Treatment Further Reduce Coronary Events and Myocardial Perfusion Abnormalities Compared With Usual-Care Cholesterol-Lowering Drugs in Coronary Artery Disease

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OBJECTIVES The purpose of this study was to determine if combined intense lifestyle and pharmacologic lipid treatment reduce myocardial perfusion abnormalities and coronary events in comparison to usual-care cholesterol-lowering drugs and whether perfusion changes predict outcomes.

BACKGROUND Lifestyle and lipid drugs separately benefit patients with coronary artery disease (CAD).

METHODS A total of 409 patients with CAD, who underwent myocardial perfusion imaging by dipyridamole positron emission tomography at baseline and after 2.6 years, had quantitative size/severity of perfusion defects measured objectively by automated software with follow-up for five additional years for coronary artery bypass graft, percutaneous coronary intervention, myocardial infarction, or cardiac death. Patients were categorized blindly according to prospective, predefined criteria as "poor" treatment without diet or lipid drugs, or smoking; "moderate" treatment on American Heart Association diet and lipid-lowering drugs or on strict low-fat diet (<10% of calories) without lipid drugs; and "maximal" treatment with diet <10% of calories as fat, regular exercise, and lipid active drugs dosed to target goals of low-density lipoproteins <2.3 mmol/l (90 mg/dl), high-density lipoproteins >1.2 mmol/l (45 mg/dl), and triglycerides <1.1 mmol/l (100 mg/dl).

RESULTS Over five years, coronary events occurred in 6.6%, 20.3%, and 30.6% of patients on maximal, moderate, and poor treatment, respectively (p = 0.001). Size/severity of perfusion abnormalities significantly decreased for patients receiving maximal treatment and increased for patients undergoing moderate and poor treatment (p = 0.003 and 0.0001, respectively). Combined intense lifestyle change plus lipid active drugs and severity/change of perfusion abnormalities independently predicted cardiac events.

CONCLUSIONS Intense lifestyle and pharmacologic lipid treatment reduce size/severity of myocardial perfusion abnormalities and cardiac events compared with usual-care cholesterol-lowering drugs. Perfusion changes parallel treatment intensity and predict outcomes. (J Am Coll Cardiol 2003;41:263–72) © 2003 by the American College of Cardiology Foundation

Randomized arteriographic trials have demonstrated that cholesterol-lowering drugs cause a modest regression of coronary artery stenoses and a disproportionately greater decrease in cardiac events. Dietary-lifestyle trials also show improved survival or regression.

However, whether combined intense lifestyle and pharmacologic lipid treatment are better than usual-care

cholesterol-lowering drugs in coronary artery disease (CAD) has not been determined. A severe limitation in addressing this question stems from the difficulty of randomizing patients who are highly motivated or unmotivated to make intense, long-term lifestyle changes necessary for observing significant differences when event rates are low. In our experience, highly motivated patients do not accept randomized assignment to a control group but will undertake strict lifestyle changes on their own if assigned to the control group or refuse to participate in the study. Others are motivated to make lifestyle changes but opposed to lipid active medications regardless of randomized assignment. Still others are not motivated to make long-term intense lifestyle changes and will not adhere to a strict regimen with or without medications regardless of randomized assignment. Additional complexity arises from highly variable

Abbreviations and Acronyms

CABG	=	coronary artery bypass graft
CAD	=	coronary artery disease
HDL	=	high-density lipoproteins
LDL	=	low-density lipoproteins
LV	=	left ventricle
MI	=	myocardial infarction
PCI	=	percutaneous coronary intervention
PET	=	positron emission tomography

responses to different cholesterol-lowering drugs or doses that preclude standardization of their effects relative to lifestyle.

Therefore, a randomized design to study this question may fail to include highly motivated subjects or may include subjects who will adhere to strict risk factor reduction even if assigned to a control group. To the extent that such patients will not accept randomization, the remaining subjects willing to be randomized more likely lack motivation for making intense long-term lifestyle changes if assigned to the maximally treated group. In either instance, randomizing patients introduces potential bias from poorly motivated subjects assigned to the maximal treatment group and motivated patients assigned to the control group with consequent little difference between groups and negative results. Although some people may not undertake intense lifestyle changes, for the substantial number that will, whether combined intense lifestyle and pharmacologic treatment add benefit over usual-care cholesterol-lowering drugs is unknown.

Therefore, this prospective cohort study used predefined, objective, blindly applied criteria for treatment classification with follow-up over five years for cardiac events, cardiac deaths, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), and changes in myocardial stress perfusion abnormalities by positron emission tomography (PET) to test the following two hypotheses: (a) intense risk factor treatment combining very low-fat low-calorie food, weight loss, monthly follow-up, and regular exercise in addition to single or multiple lipid active drugs dosed to target goals reduces cardiac events, deaths, revascularization procedures, and size/severity of myocardial perfusion abnormalities compared with usual-care cholesterol-lowering drugs in CAD; (b) over long-term follow-up, changes in myocardial perfusion by non-invasive PET parallel the intensity of treatment and predict coronary events before they occur as markers of progression/regression guiding treatment.

METHODS

Study patients. A total of 409 consecutive, unselected patients with stable CAD, who underwent rest-dipyridamole myocardial perfusion PET scans at baseline and at follow-up averaging 2.6 years later, were followed for five more years for cardiac events. As approved by the

University of Texas Committee for Protection of Human Subjects, patients signed a consent form for each PET study and for the intense maximal treatment program if they chose to enroll in it. Patients in the moderate and poor treatment groups did not sign any additional consent form for treatment because they did not undertake the intense treatment program.

Having two sequential cardiac PET studies was the criterion for inclusion in the study. At the follow-up PET study, patients were objectively categorized by blinded observers who used prospectively predefined, objective criteria into three groups based on intensity of medical therapy during the interval between the two PET studies. Patients in the "poor" treatment group were not on a diet or a lipid active medication or were actively smoking. Patients in the "moderate" treatment group were instructed in an American Heart Association diet with 20% to 30% of calories as fat and lipid active drugs, or were on a strict diet with <10% of calories as fat without lipid-lowering drugs. Patients in the maximal treatment group were on the following dietary-lifestyle and pharmacologic regimen, previously described in detail (1) and summarized as follows: 1) 10 to 20 g of fat/day; 2) 60 to 80 g of protein from non-fat or low-fat dairy products, egg whites, vegetable protein burgers or protein supplements, fish, skinned chicken breast or turkey breast, extra lean pork or beans, all baked or grilled, not fried; 3) whatever caloric-carbohydrate restriction was required to achieve ideal weight; 4) unlimited vegetables and salads; 5) exercise 30 min or more, 4 to 5 days/week, doing whatever activity maintained adherence; 6) one or more lipid active drugs dosed to goals of low-density lipoproteins (LDL) <2.3 mmol/l (90 mg/dl), high-density lipoproteins (HDL) >1.2 mmol/l (45 mg/dl), and triglycerides <1.1 mmol/l (100 mg/dl); 7) aspirin daily; 8) monthly follow-up for detailed food history, lifestyle review, and medication adjustment until the aforementioned goals were reached; and 9) antianginal and/or blood pressure medications as needed, including beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and nitrates.

Diabetes was defined as a fasting plasma glucose level >140 mg/dl, systemic hypertension as a brachial artery pressure >140/90 mm Hg, hypercholesterolemia as fasting total cholesterol >200 mg/dl, hypertriglyceridemia as triglycerides >200 mg/dl, and low HDL if <35 mg/dl.

Patients with only 12 months or less between baseline and follow-up PET, defined as inadequate for predicting long-term events from PET changes, were analyzed as a separate group for PET end points. Lifestyle changes take time for testing long-term adherence as well as for biologic effects of lifestyle changes. Our experimental design separates the long-term effects of lifestyle change from previous living habits, the effects of which are mixed during the first year after the lifestyle changes. Considering this first year group separately provides an internal control for reproducibility of PET measurements. Patients with PCI or CABG in the interval between the two PET studies were consid-

ered separately as an internal comparison because the intervention would alter myocardial perfusion separately from risk factor treatment. Patients with severe liver or renal dysfunction or with coronary revascularization during the previous six months were excluded.

Follow-up for clinical outcome was obtained at a mean interval of five years after the final PET scan based on medical records, clinic or telephone interview, and/or a national death certificate registry by personnel blinded to patient group assignment. If the patient could not be contacted, a relative and/or the patient's physician was interviewed. If these efforts were not successful, a letter was sent with a questionnaire and a request for the patient to call the PET center. For the remaining few patients without complete follow-up information, a national death certificate registry was reviewed. Each patient or source was queried about cardiovascular events and procedures, including death, myocardial infarction (MI), PCI, CABG, and stroke as end points of the study. For deaths, cause of death was obtained from hospital records, the patient's physician, or death certificates.

PET imaging. As previously described (2–7), PET imaging was carried out using the University of Texas designed, Posicam, multislice tomograph with a reconstructed resolution of 10 mm full width at half maximum. Transmission images to correct for photon attenuation contained 100 to 150 million counts. Emission images obtained after intravenous injection of 18 mCi of cyclotron produced nitrogen-13 [^{13}N] contained 20 to 40 million counts.

At 40 min after administration of the first dose of ammonia, dipyridamole (0.142 mg/kg/min) was infused for 4 min. Four minutes after infusion was complete, a second dose of 18 mCi of nitrogen-13 ammonia was injected intravenously. Four minutes later to allow blood pool clearing, PET imaging was repeated by the same protocol as for the resting study. For angina, aminophylline (125 mg) was given intravenously. As an interim midpoint assessment, the follow-up PET scan was obtained at a mean of 2.6 years after the baseline PET.

Automated quantitative analysis of PET images. Completely automated analysis of severity/size of PET abnormalities was carried out using previously described software (2–7). A three-dimensional restructuring algorithm generates true short- and long-axis views from PET transaxial cardiac images, perpendicular to and parallel to the long axis of the left ventricle (LV). Circumferential profiles are used to reconstruct three-dimensional (3D) topographic views of the LV showing relative regional activity distribution divided into lateral, inferior, septal, and anterior quadrant views of the 3D topographic display (Fig. 1).

Mean activity in each quadrant is normalized to the maximum 2% of pixels in the whole heart data set. Regions of each quadrant are identified having values outside 97.5% confidence intervals (CI) or 2.5 SD outside normal values of 10 normal volunteers without risk factors or family history, and percent of circumferential profile units outside 97.5% CI is calculated automatically.

PET end points. End points measured automatically on PET images were as follows:

1. Size of perfusion defects quantified as percent of the cardiac image outside 97.5% CI or 2.5 SD of normal control subjects.
2. Severity quantified as the lowest quadrant average relative activity, i.e., average relative activity for the quadrant having the lowest average activity of anterior, septal, lateral, and inferior quadrants for each subject. The quadrant with the lowest or minimum relative activity contains the perfusion defect(s) and quantifies relative severity of segmental perfusion abnormalities at rest and after dipyridamole stress.
3. Combined size and severity of perfusion defects were defined as percent of cardiac image with relative activity of less than 60% of maximum activity (100%) which is 3 SD below the mean maximum activity of normal control subjects.

Clinical end points. A five-year follow-up was obtained for a hard clinical end point defined as death from any cause, cardiac death, MI, stroke, PCI, or CABG.

Statistical analysis. Differences in primary PET end points and other continuous variables were analyzed using analysis of variance with Bonferroni-Dunn post hoc correction in StatView software (Abacus Concepts Inc., Berkeley, California). Data are reported as mean $\pm$ 1 SD. For discrete variables, significant differences between groups were determined by chi-square test or Fisher exact test. A single stepwise multivariate logistic regression analysis was carried out on all subjects in the maximal, moderate, and poor treatment groups, including all 46 clinical and PET measured variables in order to identify the independent predictors of cardiac death, non-fatal MI, PCI, CABG, or stroke using Excel and/or Statistica software. For a two-sided *t* test at 5% significance level and an estimated SD for change from baseline severity of 16% based on previous studies, a sample size of 48 patients in each group would have 95% power to detect a difference of 12% mean severity change in myocardial perfusion for a total of 144 patients.

RESULTS

Of 409 patients with baseline and follow-up PET scans, 45 had a revascularization procedure in the interval between the first and the second PET that would alter myocardial perfusion separately from lifestyle and pharmacologic therapy; and 38 had a follow-up PET scan within 12 months after baseline, defined as inadequate for long-term follow-up. The remaining 326 patients were assigned to one of the three chronic medical treatment groups as follows: 92 in the poor, 142 in the moderate, and 92 in the maximal treatment groups. The 45 patients with revascularization between the two PET scans and the 38 patients with less than a year
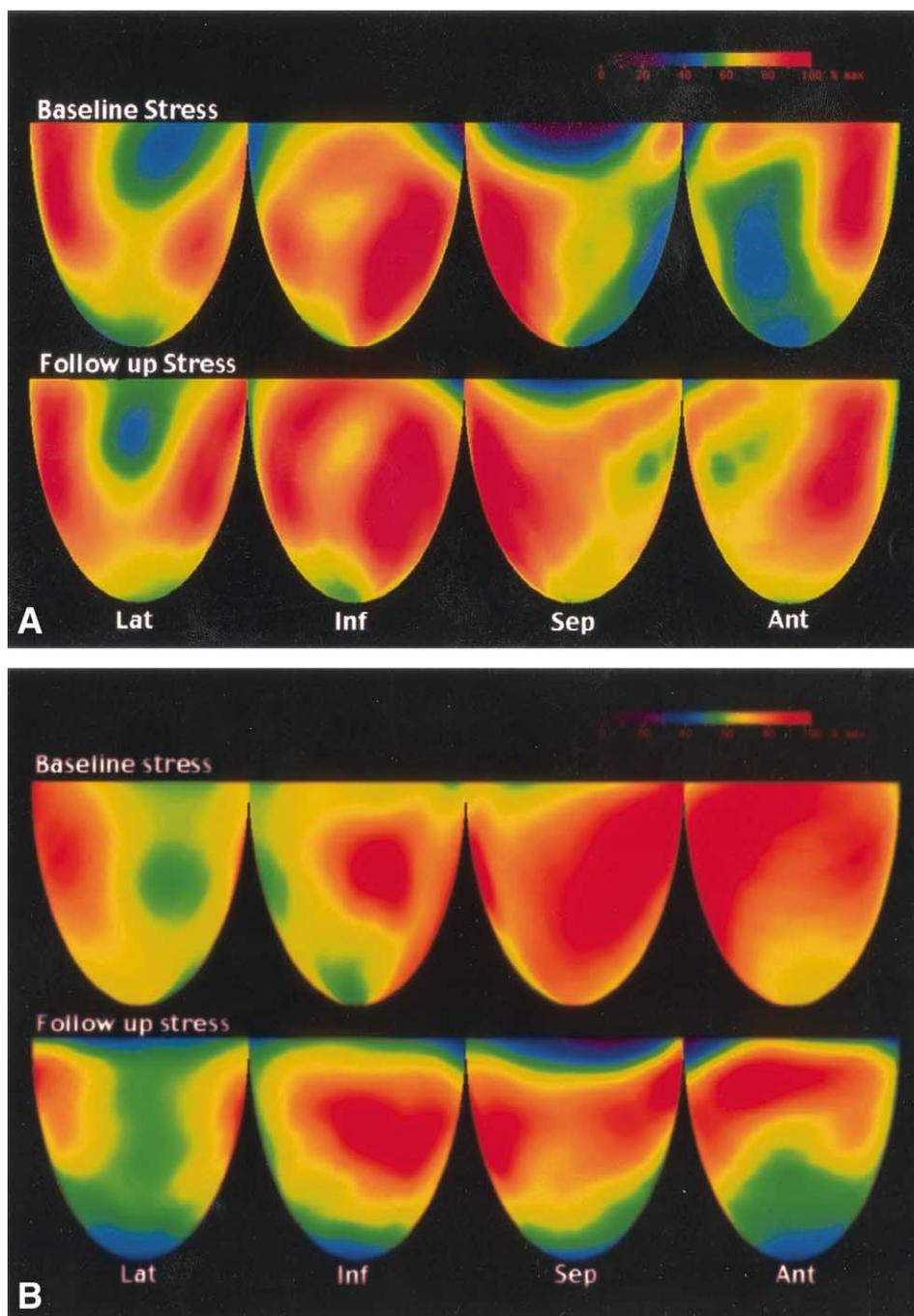
Figure 1. Examples of dipyridamole positron emission tomography with improved perfusion indicating regression **(A)** and with worsening perfusion indicating progression of coronary artery disease **(B)**. Three-dimensional topographic views from **left to right** are lateral (Lat), inferior (Inf), septal (Sep), and anterior (Ant) views. The **upper row** is after dipyridamole at baseline, and the **lower row** is after dipyridamole at follow-up. Resting perfusion images were normal (not shown). **Red** = the highest flow; **yellow** = intermediate; **green and blue** = progressively lower perfusion in continuous graded steps according to the color bar.

between PET scans were analyzed as separate groups for comparison to the perfusion changes in the maximal, moderate, and poor treatment groups.

Baseline clinical characteristics in the three treatment groups were comparable for age, gender, coronary risk factors, history of MI, and left ventricular ejection fraction as listed in Table 1. Baseline size and severity of perfusion defects were modestly but significantly larger and more

severe in the maximal therapy group, with p = 0.01 indicating more severe CAD than in moderate or poor treatment groups.

Lipid levels, blood pressure, and medications at follow-up PET for the three groups are shown in Table 2. There were significant differences among the groups in total cholesterol, LDL, triglyceride levels, weight changes, and adherence to an exercise regimen, reflecting the spectrum of treatment

Table 1. Selected Baseline Characteristics by Treatment Group

Baseline Characteristics	Maximal (n = 92)	Moderate (n = 142)	Poor (n = 92)	p Value
Age	59 ± 8.2	57 ± 9.7	58 ± 8.9	0.25
No. (%) of patients				
Men	87 (94)	122 (86)	83 (90)	0.10
Women	5 (6)	20 (14)	9 (10)	0.10
Systemic hypertension	38 (41)	51 (36)	34 (37)	0.69
Diabetes mellitus	3 (3)	14 (10)	4 (4)	0.08
Family history of CAD	70 (76)	93 (65)	59 (64)	0.14
Hypercholesterolemia	69 (75)	110 (77)	76 (82)	0.43
Hypertriglyceridemia	16 (17)	23 (16)	9 (10)	0.27
Low HDL	45 (49)	59 (41)	33 (36)	0.19
Myocardial infarction	23 (25)	49 (34)	22 (24)	0.13
LVEF %	55 ± 11	57 ± 12	58 ± 10	0.47
Weight, lb	178 ± 28	181 ± 28	183 ± 35	0.77

CAD = coronary artery disease; HDL = high-density lipoproteins; LVEF = left ventricular ejection fraction.

intensity, from maximal treatment combining intense lifestyle changes, to usual-care lipid active drugs, to undertreatment commonly found in clinical practice. The small differences in HDL were of uncertain significance, with slightly higher values in the poorly treated group. Blood pressure was similar in the three groups and not significantly changed from baseline values. There was no significant difference in the use of aspirin or ACE inhibitors. Beta-blockers were less commonly used in the poor treatment group, paralleling dietary and pharmacologic undertreatment of patients not participating in the program of combined lifestyle plus treatment with lipid drugs; however, absence of beta-blockers did not predict cardiovascular events owing to the small dispersion of beta-blocker treatment between groups and the more prominent effects of other treatment.

Changes in myocardial perfusion by PET. Time from baseline to follow-up PET averaged 2.6 ± 1.4 years. Figure 1 illustrates regression with improved myocardial perfusion

in a maximal treatment patient (Panel A) and progression with worsening in a poor treatment patient (Panel B). Mean change from the baseline to follow-up PET (PET2 − PET1) of absolute values of PET end points, their SDs, and p values are listed for each group in Table 3.

Figure 2 shows for each group the relative percent change from baseline of the severity (lowest quadrant average activity) of myocardial perfusion abnormalities after dipyridamole stress. In maximal treatment patients, lowest quadrant activity increased, indicating improvement in severity of the perfusion abnormality on the final study compared with baseline. In the moderate treatment group, lowest quadrant activity decreased insignificantly, indicating stability. In the poor treatment group, this lowest activity decreased further, indicating significantly more severe or worsening abnormality in the final study compared with baseline. Differences in changes between groups were significant (p = 0.0001).

Table 2. Follow-Up Characteristics by Treatment Group

	Maximal (n = 92)	Moderate (n = 142)	Poor (n = 92)	p Value
Lipid profile				
Total cholesterol (mmol/l) (mg%)	3.62 ± 0.5 (140 ± 20)	4.75 ± 0.9 (184 ± 35)	5.84 ± 1.1 (226 ± 45)	< 0.0001
LDL (mmol/l) (mg%)	1.91 ± 0.4 (74 ± 16)	2.87 ± 0.8 (111 ± 34)	3.69 ± 1.1 (143 ± 44)	< 0.0001
HDL (mmol/l) (mg%)	1.26 ± 0.2 (49 ± 11)	1.16 ± 0.3 (45 ± 15)	1.31 ± 0.4 (51 ± 16)	0.05
Triglycerides (mmol/l) (mg%)	0.98 ± 0.3 (87 ± 30)	1.78 ± 1 (158 ± 93)	1.90 ± 1 (169 ± 93)	< 0.0001
Systolic blood pressure (mm Hg)	126 ± 18	126 ± 17	129 ± 15	0.3
Diastolic blood pressure (mm Hg)	71 ± 11	70 ± 10	73 ± 11	0.19
Regular exercise (%)	69 (75)	74 (52)	42 (45)	0.01
Weight change, lb	−5.8 ± 10	+0.2 ± 13	+3.3 ± 10	< 0.0001
No. (%) medications				
Statins	82 (89)	92 (64)	14 (15)	< 0.0001
ACE inhibitors	21 (22)	26 (18)	9 (10)	0.057
Beta-blockers	28 (30)*	40 (28)*	14 (15)	0.03
ASA	70 (76)	90 (63)	67 (73)	0.08

*No significant difference good vs. maximal treatment (p value = 0.9).
ACE = angiotensin-converting enzyme; ASA = acetylsalicylic acid; HDL = high-density lipoproteins; LDL = low-density lipoproteins.

Table 3. Absolute Changes in Perfusion Abnormalities: Final PET − Baseline PET

PET End Point	Maximal	Moderate	Poor	ANOVA (n = 326)	Short*	Procedure	ANOVA (n = 409)
Lowest quadrant average count, % of maximum	+3.1 ± 7.7	−0.5 ± 7.6	−1.9 ± 7.2	<0.0001	−0.5 ± 8.1	+2.3 ± 11	0.0002
% of LV outside 2.5 SDs	−0.02 ± 0.1	+0.03 ± 0.1	+0.03 ± 0.1	0.003	+0.01 ± 0.1	+0.005 ± 0.1	0.02
% of LV with activity <60% of maximum	−0.51 ± 0.1	+0.006 ± 0.1	+0.03 ± 0.1	<0.0001	−0.004 ± 0.1	−0.03 ± 0.1	0.0002

*The group with a short interval time. Numbers are mean ± SD.
ANOVA = p value by analysis of variance; LV = left ventricle; PET = positron emission tomography; SD = standard deviation.

For patients undergoing revascularization procedures in the interval between baseline and the follow-up PET study, severity of defects decreased but was not greater than improvement in the maximal therapy group not undergoing revascularization.

Figure 3 shows for each group the relative percent change in size of myocardial perfusion abnormalities (percent of the LV outside 2.5 SD of normal control subjects) after dipyridamole stress. In the maximal treatment group, size of myocardial perfusion defects decreased, indicating improvement. In the moderate and poor treatment groups, size of perfusion abnormalities increased, indicating a larger perfusion defect. Difference in changes between groups was significant (p = 0.003). In the revascularization group, size of perfusion defects did not change from baseline despite decreased severity, suggesting residual diffuse disease.

Figure 4 shows for each group the relative percent change in combined size and severity end point (percent of the LV with activity less than 60% of maximum activity). In the maximal treatment patients, percent of LV below 60% of maximum activity decreased, indicating improvement of the perfusion abnormalities. In the moderate treatment pa-

tients, percent of LV below 60% of maximum activity showed insignificant changes, indicating stability. In the poor treatment group, percent of LV below 60% of maximum increased further, indicating more severe or worsening abnormalities. Differences in changes between groups for this combined size and severity end point were significant (p = 0.0001).

Interestingly, in the revascularization group, this combined end point of size and severity increased, indicating worsening of mild perfusion abnormalities, whereas the severest abnormality improved, explained by a reduction of localized stenoses that makes the effects of residual diffuse disease more apparent as a milder but larger defect.

Cardiovascular events. At a mean of five years after the follow-up PET scan, clinical follow-up for mortality was obtained in all patients. The composite clinical end point of cardiac death, non-fatal MI, PCI, CABG, or stroke was 6.6%, 20.3%, and 30.6% in the maximal, moderate, and poor treatment groups respectively, shown in Figure 5 (p = 0.001). This prevalence corresponds to a relative reduction in events of 67% in the maximal treatment group compared with the moderate treatment group and of 78% compared
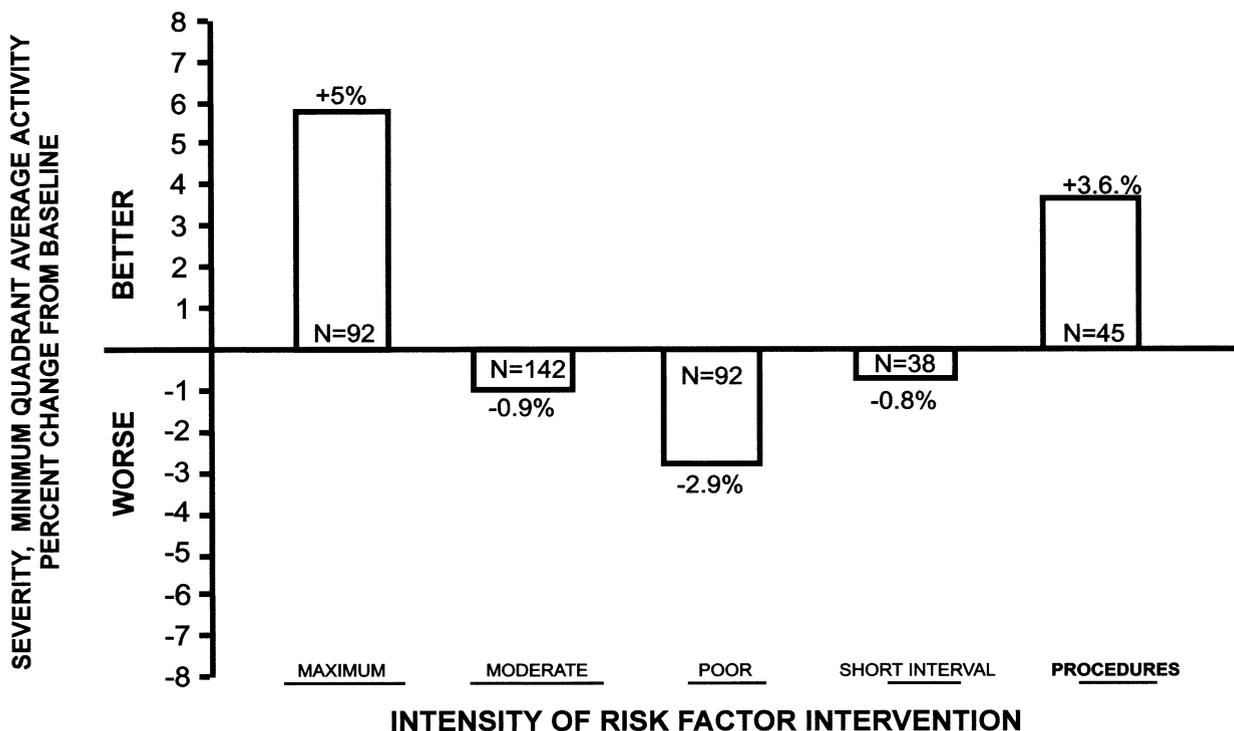

Figure 2. Changes in the quantitative severity of myocardial perfusion abnormalities by dipyridamole positron emission tomography.
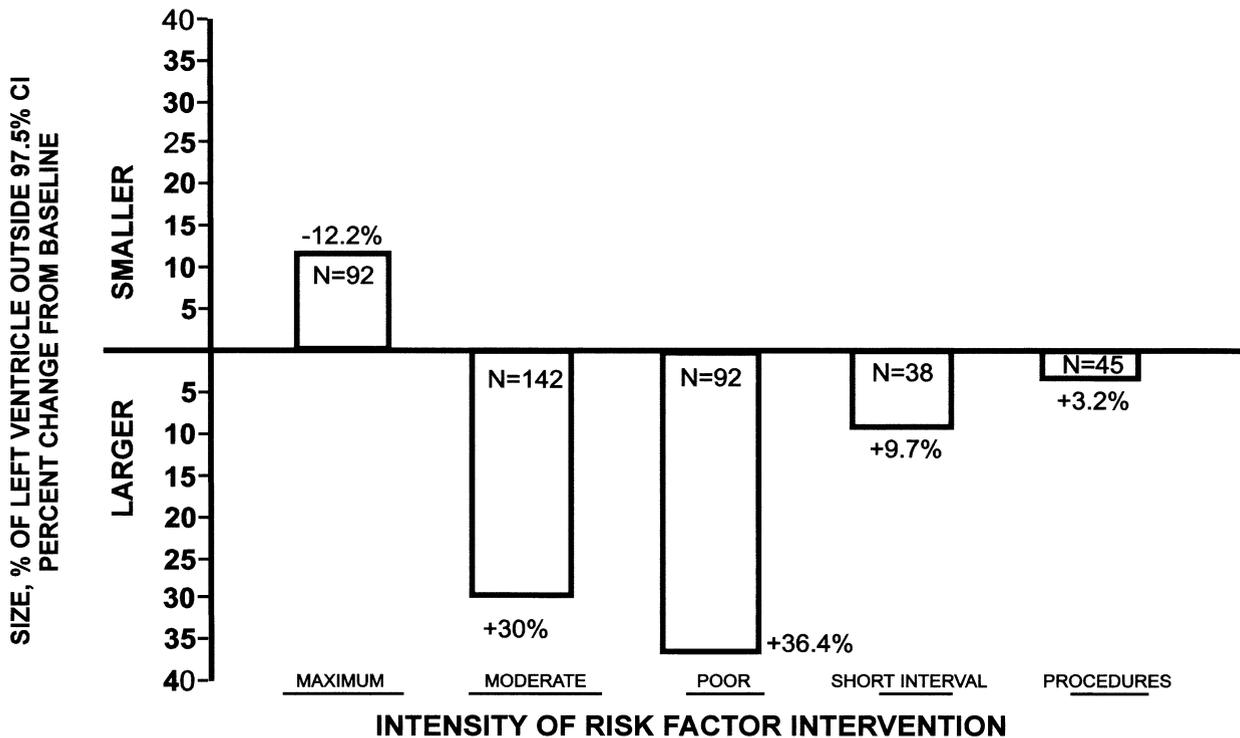
Figure 3. Changes in the size of myocardial perfusion abnormalities.

with the poor treatment group (for both, p = 0.001). Revascularization procedures were significantly less frequent in the maximal treatment group compared with the moderate and poor treatment groups (p = 0.007). Deaths of any cause and non-fatal MI were observed in 3.3%, 15%, and 13% in the maximal, moderate, and poor treatment groups respectively (p = 0.02). We could not obtain follow-up information on non-fatal events in 38 patients (11.7%) with no recorded death certificate, who were therefore probably alive; these patients were distributed among the treatment
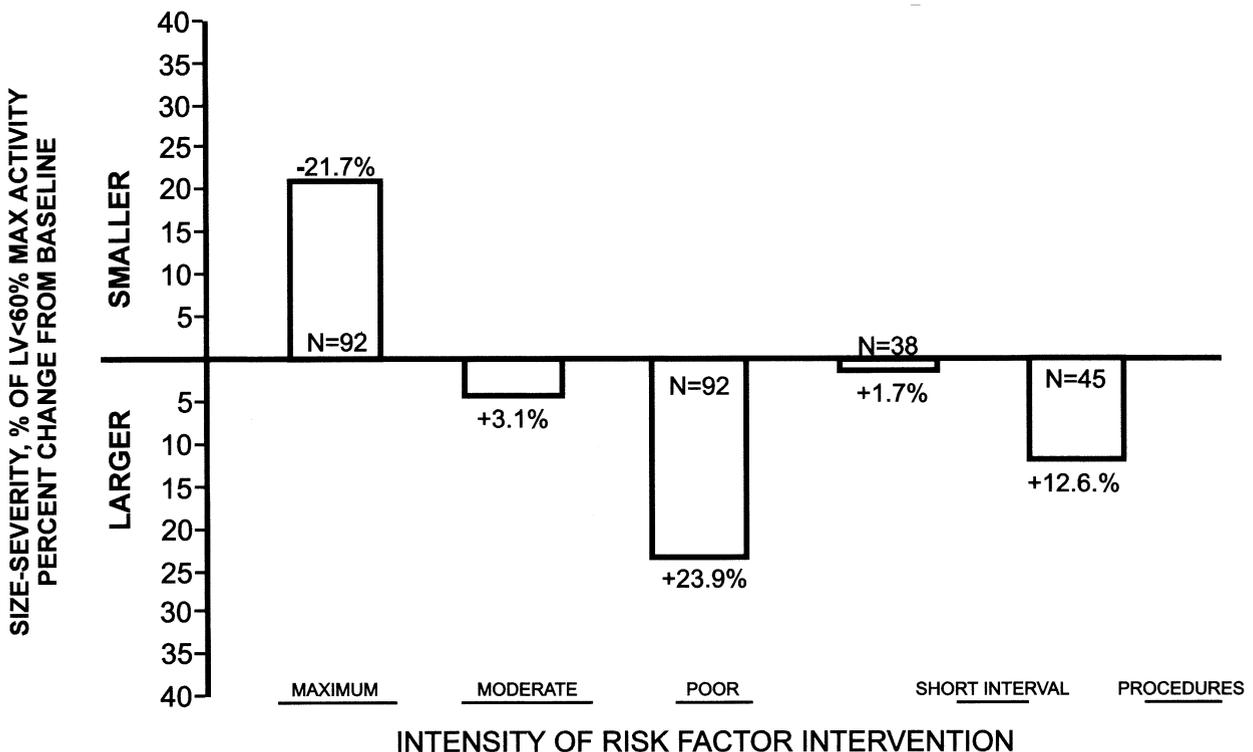

Figure 4. Changes in the combined size and severity of myocardial perfusion abnormalities.
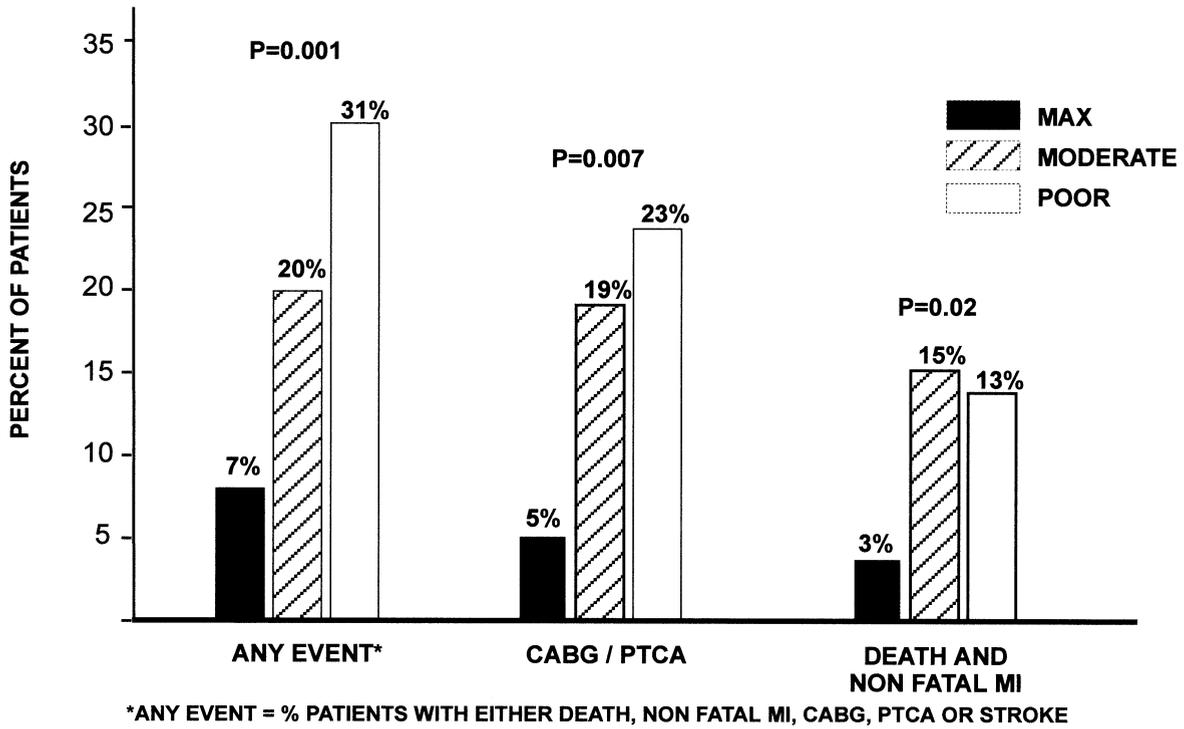
Figure 5. Cardiovascular events at the end of five-year follow-up. CABG = coronary artery bypass graft; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

groups as follows: 2/92 (2.2%) of the maximal treatment group, 19/142 (13.4%) of the moderate treatment group, and 17/92 (18.5%) of the poor treatment group.

Figure 6 graphs cumulative frequency distribution for combined events over five-year follow-up. Differences among groups were significant with p = 0.001 due principally to the difference between the maximal treatment group and the other two groups. The moderate treatment group
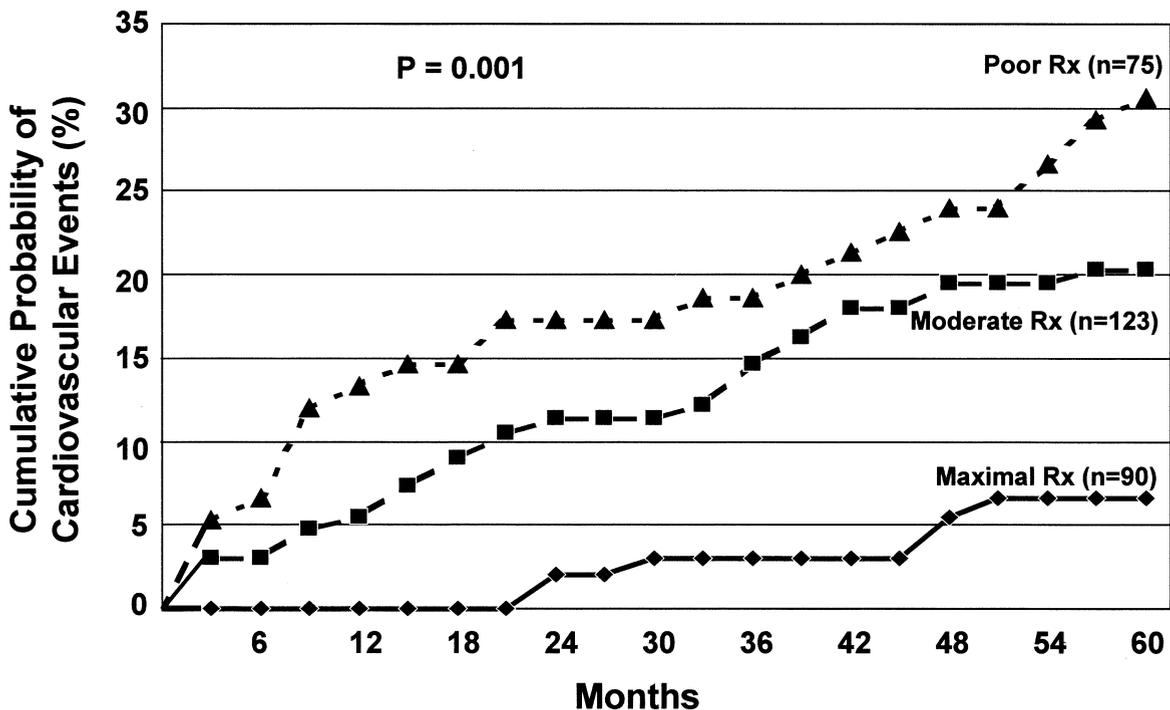

Figure 6. Cumulative probability of cardiovascular events during five-year follow-up. See text for explanation of values of n and size of treatment (Rx) groups.

Table 4. Independent Predictors of Cardiovascular Events at 5 Years Follow-Up by Stepwise Multivariate Logistic Regression Analysis

	Odds Ratio	95% CI	p Value
Treatment factors			
Combined lifestyle + lipid drugs	0.53	0.23–0.89	0.009
Regular exercise	0.39	0.17–0.52	< 0.001
Statin therapy	0.40	0.26–0.85	0.006
Risk factors			
LDL mg%	2.72	2.38–2.96	0.002
HDL mg%	0.58	0.27–0.96	0.02
Diabetes mellitus	2.22	1.53–2.23	0.009
Family history of CAD	1.62	1.12–1.80	0.01
PET factors			
Combined size-severity of perfusion defect	4.87	2.71–5.32	< 0.001
Severity of perfusion defect	2.59	2.37–2.93	0.008
Size of perfusion defect	1.92	1.52–2.14	0.03
Worsening in size-severity of perfusion defect	1.36	1.11–1.56	0.01

CAD = coronary artery disease; CI = confidence intervals; HDL = high-density lipoproteins; LDL = low-density lipoproteins; PET = positron emission tomography.

had a 34% relative reduction in cardiovascular events compared with the poor therapy group, which, however, failed to reach statistical significance (p = 0.13).

By stepwise multivariate logistic regression analysis shown in Table 4, independent predictors of the combined end point (MI, death, PCI, or CABG) were as follows: severity of myocardial perfusion abnormalities on dipyridamole PET scans, change in myocardial perfusion abnormalities between the baseline and follow-up PET scans, combined intense lifestyle changes plus lipid active drugs, lipid active medications, regular exercise, LDL and triglyceride levels, and diabetes or coronary heart disease in a mother, father, or sibling.

Because one criterion for entry into this study included paired baseline and follow-up PET, we followed patients for five additional years after the second PET to determine the predictive value of PET changes in relation to treatment intensity. If cardiac events between the paired PET studies are included in the analysis (which excludes deaths because a follow-up PET requires survival), the percentage of patients with events in each group (maximal 6.6%, moderate 21.1%, poor 30.6%) is comparable to the five-year follow-up after the second PET. Only three cardiac events (2 CABG, 1 PCI) occurred among the 17 smokers in the poor group by definition; because 17.6% of smokers and 16.5% of non-

smokers had cardiovascular events (NS, p = 0.9), the differences between the groups cannot be explained by smoking owing to the small number of smokers.

Table 5 lists the number of events or procedures during the PET 1 to PET 2 interval; there is an insignificant trend for fewer events and procedures in the maximal and moderate treatment groups versus the poor treatment groups (p = 0.07). However, none of the differences in events or procedures among the treatment groups during the PET 1 to PET 2 interval are significant.

DISCUSSION

This study is the first to demonstrate with long-term follow-up that intense risk factor treatment combining very low-fat food, weight control, and regular exercise plus lipid active drugs dosed to target goals markedly reduces cardiovascular events, deaths, revascularization procedures, and size/severity of stress-induced myocardial perfusion abnormalities compared with usual-care lipid active drugs. The data also suggest that approximately 2 to 2.5 years of intense combined treatment are required before events and mortality decrease. During this initial period of intense treatment, changes in myocardial perfusion by PET show responses to treatment and predict outcomes over the subsequent five years as a guide to treatment before cardiac events occur.

These findings by non-invasive PET are consistent with invasive arteriographic lipid trials showing that changes in arteriographic severity also predict risk of cardiovascular events.

Rationale for combined lifestyle and pharmacologic therapy. In randomized trials of statin drugs, placebo control groups following an American Heart Association diet with 20% of calories from fat showed overall progression of CAD and coronary events. However, dietary trials have shown regression, stability, and/or reduction in cardiovascular events compared with non-diet controls.

Low-fat diet and weight (calorie) control may be important separate from fasting cholesterol levels because of the postprandial surge of triglyceride and very low-density lipoproteins. The postprandial lipoprotein surge is abnormally high in patients with CAD (8) or children of parents with CAD (9), is a powerful predictor of progressive disease (10), and is not altered by statin monotherapy (11). Thus, diet may contribute substantially to cardiovascular risk

Table 5. Events for the Interval PET1–PET2 in All 409 Patients (Without Exclusions)

Events (No. of Patients)	Maximal (n = 106)	Moderate (n = 173)	Poor (n = 130)	p Value
Non-fatal MI	1 (1)	6 (6)	3 (3)	0.33
PTCA	13 (10)	12 (11)	18 (16)	0.15
CABG	4 (4)	3 (3)	5 (5)	0.48
Total revascularizations	17 (12)	15 (12)	23 (21)	0.07
Any cardiovascular event*	18 (12)	21 (15)	26 (21)	0.22

*Any cardiovascular event = number of non-fatal MI, CABG, PTCA, or stroke.
CABG = coronary artery bypass graft; MI = myocardial infarction; PET = positron emission tomography; PTCA = percutaneous transluminal coronary angioplasty.

independent of and in addition to fasting lipid levels in patients taking statin drugs.

Our study demonstrates for the first time the feasibility and benefits in clinical practice of combining intense lifestyle changes—including strict low-fat diet, regular exercise, and weight control—with one or more lipid active drugs dosed to target lipid levels, resulting in a mean LDL of 1.9 mmol/l (74 mg/dl), triglycerides of 0.98 mmol/l (87 mg/dl), and HDL of 1.3 mmol/l (49 mg/dl) in the maximal therapy group. The benefits include significantly improved myocardial perfusion and a 67% reduction of major adverse cardiovascular events compared with usual-care lipid-lowering drugs despite more severe baseline myocardial perfusion abnormalities in the maximal treatment group. The moderate therapy group in this study had mean LDL of 2.9 mmol/l (111 mg/dl), comparable with mean LDL levels in treated patients of many statin trials and with current treatment standards. However, adverse cardiac events were significantly greater in this group receiving standard lipid treatment compared with the maximally treated group combining intense lifestyle changes plus pharmacologic lipid lowering.

Study limitations. Lack of randomization is a limitation of the study. However, the difficulties of randomization are formidable for such comprehensive, intense lifestyle changes over long time periods with highly variable patient motivation that may invalidate the intent of randomization and introduce other bias. Moreover, our subjects were consecutive, unselected patients having baseline and follow-up PET representing the diversity characteristic of subjects with CAD in clinical practice. They were categorized objectively by blinded observers using prospective, predefined criteria, had complete follow-up for hard cardiovascular events, and had size/severity of myocardial perfusion abnormalities objectively measured by automated software.

There were no significant differences in baseline characteristics among the groups except for significantly worse baseline myocardial perfusion abnormalities in the maximal treatment group, indicating more severe CAD that would tend to reduce differences between the groups.

Our study cannot identify the relative importance of lifestyle or its components alone versus medications. We have demonstrated the basic concept that combined intense lifestyle and pharmacologic lipid treatment have substantial added benefit over usual-care cholesterol-lowering drugs. Several differently designed studies would be required to address the relative contribution of lifestyle, its components or intensity, and fixed dose or dose-to-goal cholesterol-lowering drugs.

Finally, clinical follow-up for non-fatal events was not complete. However, because most of the patients without follow-up for non-fatal events, 36 of the 38, were in the moderate and poor treatment groups, complete follow-up on them would only have added more non-fatal events to the moderate and poor treatment groups, thereby making

the differences from the maximal treatment group even more significant than observed. All the statistical analyses involving non-fatal events were done on the 88.3% of the patients for whom follow-up on non-fatal events was obtained.

CONCLUSIONS

Combined very low-fat diet, weight control, regular exercise, monthly follow-up, and one or more lipid active drugs dosed to target lipid levels of LDL <2.3 mmol/l (90 mg/dl), HDL >1.2 mmol/l (45 mg/dl), and triglycerides <1.1 mmol/l (100 mg/dl) as "maximal" therapy markedly reduces cardiovascular events, deaths, revascularization procedures, and size/severity of stress-induced myocardial perfusion abnormalities compared with usual-care cholesterol-lowering drugs in CAD, the progression or regression of which can be followed non-invasively by dipyridamole-PET to assess treatment effectiveness and predict outcomes.

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REFERENCES

1. Gould KL. Heal Your Heart—How To Prevent or Reverse Heart Disease. New Brunswick, NJ: Rutgers University Press, 1998.
2. Demer LL, Gould KL, Goldstein RA, et al. Assessment of coronary artery disease severity by positron emission tomography: comparison with quantitative arteriography in 193 patients. Circulation 1989;79:825–35.
3. Gould KL, Martucci JP, Goldberg DI, et al. Short-term cholesterol lowering decreases size and severity of perfusion abnormalities by positron emission tomography after dipyridamole in patients with coronary artery disease: a potential noninvasive marker of healing coronary endothelium. Circulation 1994;89:1530–8.
4. Gould KL, Ornish D, Scherwitz L, et al. Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification. JAMA 1995;274:894–901.
5. Gould KL. Coronary Artery Stenosis and Reversing Atherosclerosis. 2nd ed. London: Arnold Publishers, Distributed in USA by Oxford University Press, 1999.
6. Gould KL, Nakagawa Y, Nakagawa K, et al. Frequency and clinical implications of fluid dynamically significant diffuse coronary artery disease manifest as graded, longitudinal, base-to-apex myocardial perfusion abnormalities by noninvasive positron emission tomography. Circulation 2000;101:1931–9.
7. Sdringola S, Patel D, Gould KL. High prevalence of myocardial perfusion abnormalities on positron emission tomography in asymptomatic persons with a parent or sibling with coronary artery disease. Circulation 2001;103:496–501.
8. Patsch JR, Miesenbock G, Hopferwieser T, et al. Relation of triglyceride metabolism and coronary artery disease: studies in the postprandial state. Arterioscler Thromb 1992;12:1336–45.
9. Uiterwaal CS, Grobbee DE, Witteman JC, et al. Postprandial triglyceride response in young adult men and familial risk for coronary atherosclerosis. Ann Intern Med 1994;121:576–83.
10. Karpe F, Steiner G, Uffelman K, Olivecrona T, Hamsten A. Postprandial lipoproteins and progression of coronary atherosclerosis. Atherosclerosis 1994;106:83–97.
11. O'Keefe JH, Harris WS, Nelson J, Windsor SL. Effects of pravastatin with niacin or magnesium on lipid levels and postprandial lipemia. Am J Cardiol 1995;76:480–4.