

A Randomized Trial of a Strategy for Increasing High-Density Lipoprotein Cholesterol Levels: Effects on Progression of Coronary Heart Disease and Clinical Events

Edwin J. Whitney, MD; Richard A. Krasuski, MD; Bradley E. Personius, MD; Joel E. Michalek, PhD; Ara M. Maranian, MD; Mark W. Kolasa, MD; Erik Monick, MD; B. Gregory Brown, MD, PhD; and Antonio M. Gotto Jr., MD, DPhil

Background: The high-density lipoprotein (HDL) cholesterol level is a strong predictor of cardiovascular events in epidemiologic studies. Until recently, it has been less extensively studied as a therapeutic target.

Objective: To assess the angiographic and clinical effects of a pharmacologic strategy to increase HDL cholesterol levels.

Design: Randomized, double-blind, placebo-controlled trial conducted from 1993 to 1996.

Setting: Outpatient specialty clinic of a large U.S. military medical center.

Participants: 143 military retirees younger than 76 years of age with low HDL cholesterol levels and angiographically evident coronary disease.

Intervention: Gemfibrozil, niacin, and cholestyramine or corresponding placebos, with aggressive dietary and lifestyle intervention at baseline.

Measurements: Change from baseline to 30 months and a composite measure of clinical events that included hospitalization for angina, myocardial infarction, transient ischemic attack and stroke, death, and cardiovascular procedures.

Results: At baseline, mean (\pm SD) lipid values were as follows: total cholesterol, 5.1 ± 0.8 mmol/L (196 ± 31 mg/dL); low-density lipoprotein (LDL) cholesterol, 3.3 ± 0.7 mmol/L (128 ± 27 mg/dL); and HDL cholesterol, 0.9 ± 0.2 mmol/L (34 ± 6 mg/dL). Compared with placebo, the pharmacologically treated group experienced a

20% (95% CI, 14.8% to 24.3%) decrease in total cholesterol level, a 36% (CI, 28.4% to 43.5%) increase in HDL cholesterol level, a 26% (CI, 19.1% to 33.7%) decrease in LDL cholesterol level, and a 50% (CI, 40.5% to 59.2%) reduction in triglyceride levels. Focal coronary stenosis increased by 1.4% in the placebo group but decreased by 0.8% in the drug group (difference, -2.2 percentage points [CI, -4.2 to -0.1 percentage points]). A composite cardiovascular event end point was reached in 26% of patients in the placebo group and 13% of those in the drug group (difference, 13.7 percentage points [CI, 0.9 to 26.5 percentage points]). Side effects, particularly flushing and gastrointestinal intolerance, were more common in the drug group but rarely led to withdrawal from the study.

Limitations: The study was small and used a composite clinical outcome. Whether improvements in angiographic findings were due to reductions in LDL cholesterol or increases in HDL cholesterol was not established. Flushing may have led to inadvertent unblinding in patients who were randomly assigned to active study drugs.

Conclusions: A combination regimen aimed at increasing HDL cholesterol levels improves cholesterol profiles, helps prevent angiographic progression of coronary stenosis, and may prevent cardiovascular events in some people who exercise regularly and eat low-fat diets.

Ann Intern Med. 2005;142:95-104.

www.annals.org

For author affiliations, see end of text.

Large epidemiologic studies have repeatedly demonstrated that cardiovascular risk increases proportionally with increasing total cholesterol and low-density lipoprotein (LDL) cholesterol levels and decreasing high-density lipoprotein (HDL) cholesterol levels (1, 2). Although many studies have documented that statins, drugs that primarily reduce LDL cholesterol levels, significantly reduce the risk for cardiovascular events (3–7), prospective studies that examine the clinical effects of increasing HDL cholesterol levels have been more limited. The Coronary Drug Project first reported evidence of a mortality benefit in patients treated with niacin; however, the difference was seen long after withdrawal of the study drug, making the mechanism of benefit less clear (8). The Helsinki Heart Study (9) examined the use of gemfibrozil in primary prevention. Coronary events were reduced by 34%, but the increase in HDL cholesterol level was modest (only 11%). The Bezafibrate Infarction Prevention Trial failed to show a reduction in cardiovascular events in the composite pop-

ulation, although a recent reanalysis of the data suggests an improved outcome in patients experiencing a greater increase in HDL cholesterol level (10).

The Veterans Affairs HDL Intervention Trial (VA-HIT) (11) demonstrated a modest reduction in coronary events when gemfibrozil was used in patients with normal levels of LDL cholesterol and low levels of HDL cholesterol. The authors ascribed most of the reduction in clinical events to the improvement in HDL cholesterol, al-

See also:

Print

Editor's Notes 96
Summary for Patients I-46

Web-Only

Conversion of figures and tables into slides

Context

Most trials that address lipid management focus on reducing low-density lipoprotein (LDL) cholesterol levels rather than increasing high-density lipoprotein (HDL) cholesterol levels.

Contribution

In this double-blind trial, 143 military retirees with low HDL cholesterol levels and coronary artery disease were randomly assigned to placebo or aggressive HDL cholesterol-increasing therapy with gemfibrozil, niacin, and cholestyramine for 30 months. All participants received diet and exercise counseling. Compared with the placebo group, the treated group had a 20% decrease in total cholesterol level; a 36% increase in HDL cholesterol level; less focal coronary stenosis; fewer total cardiovascular events; and more flushing, skin rashes, and abdominal symptoms.

Cautions

The small trial had limited ability to assess clinical outcomes.

—The Editors

though the overall improvement was only approximately 6% with drug therapy. More recently, a combination of a statin (simvastatin) with niacin was found to favorably modify both HDL cholesterol and LDL cholesterol levels and reduce cardiovascular events compared with both placebo therapy and underlying treatment with antioxidants in a cohort of 160 patients with coronary disease (12). Despite a significant increase in mean HDL cholesterol levels, the overwhelming treatment effect in this study was the reduction in LDL cholesterol level (42% in the treatment group).

The most suggestive evidence of benefit from an increase in HDL cholesterol level has come from trials assessing the effect on coronary stenosis. Trials of quantitative angiography after monotherapy with fibrates (13), as well as combinations of medications that both reduce LDL cholesterol levels and increase HDL cholesterol levels (14–18), have shown an attenuation in angiographic progression. Nissen and colleagues (19) recently took this theory a step further by demonstrating that an infusion of a recombinant form of HDL, apolipoprotein A-I Milano, can lead to regression of angiographic stenosis as assessed by intravascular ultrasonography.

We undertook the Armed Forces Regression Study (AFREGS) in 1993 to determine whether coronary atherosclerosis, assessed by quantitative coronary angiography and clinical coronary events, would improve when combination drug therapy focused on increasing HDL cholesterol levels in a sample of patients with fairly normal LDL cholesterol levels and low HDL cholesterol levels. A pilot

study by Whitney and colleagues (20) showed the feasibility of this trial design, and the safety of using these drugs in combination has been previously established (21).

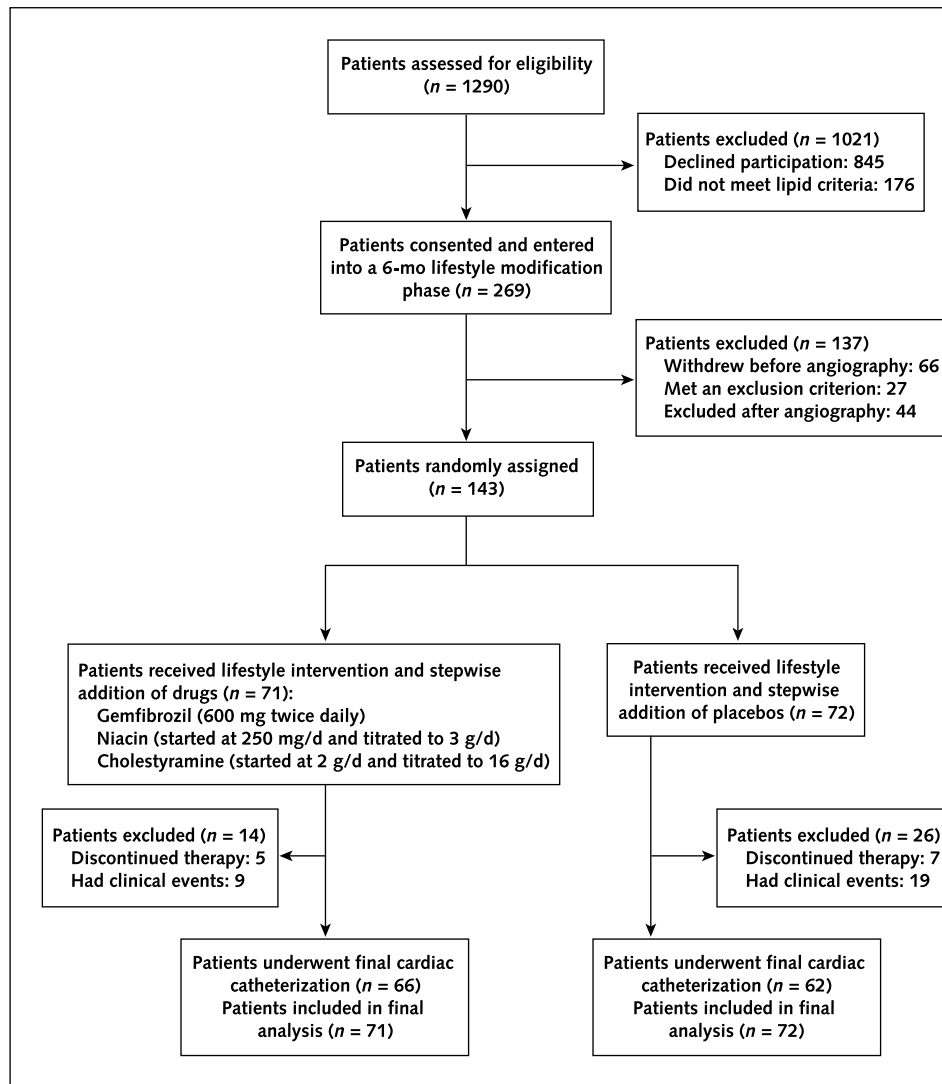
METHODS**Patients**

Participants living within a 150-mile radius of Wilford Hall Medical Center in San Antonio, Texas, who could provide written informed consent were eligible for enrollment. We recruited men and women younger than 76 years of age who had established or suspected coronary artery disease (positive results on an exercise treadmill test or classic angina) and did not have unstable symptoms. We allowed LDL cholesterol levels up to 4.1 mmol/L (160 mg/dL) with HDL cholesterol levels less than 1.0 mmol/L (40 mg/dL) after adherence to the American Heart Association (AHA) step II diet for at least 6 months. We set no lower limit to either HDL cholesterol or LDL cholesterol level. Each patient was required to have measurable stenosis between 30% and 80% of the luminal diameter within the coronary tree by caliper inspection. Patients with stenosis greater than 80% were eligible if they had a favorable prognosis based on functional testing (ability to exercise for >9 minutes on a full Bruce protocol exercise treadmill test).

Exclusions included a major vascular event (myocardial infarction, cerebrovascular accident, coronary artery bypass grafting, or other coronary catheter-based intervention) within 6 months, a history of congestive heart failure (other than in the setting of myocardial infarction), or a left ventricular ejection fraction less than 0.4 on ventriculography. Other exclusion criteria included alcohol or substance abuse within the past year, uncontrolled arrhythmias, resistant hypertension, diabetes, uncontrolled gout, uncontrolled thyroid disease, liver or gall bladder disease, renal dysfunction (creatinine concentration > 176.8 $\mu\text{mol/L}$ [>2.0 mg/dL] or proteinuria greater than 2+ by dipstick or 500 mg/24 h), uncontrolled peptic ulcer disease, or pancreatic disorders. In addition, we excluded patients taking any lipid-modifying medications within 4 weeks of randomization, heparin or coumarin-type anticoagulants, long-term oral corticosteroid therapy, or other immunosuppressive agents. We also excluded patients if they had hypersensitivity to or history of intolerance that required cessation of therapy for any component of gemfibrozil, nicotinic acid, cholestyramine, aspirin, or nitrates. Other exclusion criteria were the potential for childbearing, technically inadequate coronary arteriography for stenosis quantification, or any serious condition that we thought would compromise participation in the study or preclude survival for the duration of the study.

We thoroughly informed participants of the details of the study. Each patient voluntarily enrolled and signed an informed consent statement that the Wilford Hall Medical Center Institutional Review Board reviewed and approved.

Figure 1. Flow of patients through the study.



From screening laboratory records, we identified 1290 participant candidates and invited them to participate (Figure 1). Of the 847 patients who attended the “introductory briefing,” 671 met LDL cholesterol and HDL cholesterol entry criteria on fasting lipid analysis. Of the 269 participants who eventually provided informed consent, 55 subsequently withdrew for personal reasons, most commonly citing a fear of cardiac catheterization, and an additional 27 met an exclusion criterion. Of the 187 participants who completed the 6-month lifestyle modification phase and underwent coronary angiography, 44 were excluded after initial coronary arteriography; 27 had extensive coronary disease necessitating revascularization (percutaneous coronary intervention in 3 patients and coronary artery bypass grafting in 24 patients), and 17 had insignificant coronary disease on angiography. Thus, we eventually randomly assigned 143 patients (11% of those initially contacted) to either pharmacologic therapy or placebo.

Protocol

After inclusion and exclusion criteria were met, a 6- to 8-month run-in period was performed to ensure that patients could adhere to the prescribed diet. During this phase, all patients received diet counseling from a study dietitian, exercise guidance from an exercise specialist, and smoking cessation advice. All study participants committed to attending a bimonthly food show for training in the AHA step II diet, with reinforcing presentations from the dietitian, exercise specialist, and cardiologist that discussed cardiac risk factor modification.

We randomly assigned each participant by using a computer-generated randomization schedule. The central pharmacy held the code, and the information was not shared with physicians or patients until the completion of the protocol. Patients were randomly assigned to 1 of 2 treatment groups: pharmacologic therapy with gemfibrozil, niacin, and cholestyramine or conventional therapy. The

goal of therapy was to increase HDL cholesterol level by at least 25%. The study was double-blind and placebo-controlled. The pharmaceutical company prepared all medications and placebos, and the central pharmacy dispensed them at 30-day intervals. The pharmacologic therapy group began receiving gemfibrozil, 600 mg twice per day. Short-acting niacin was added in the third month at a dosage of 250 mg/d and was titrated to 3000 mg/d as tolerated. Cholestyramine was added in the sixth month, and the dosage was titrated to 16 g/d as tolerated. The conventional therapy group was maintained on the AHA step II diet and applicable matching placebos for the duration of the investigation. If LDL cholesterol levels exceeded 4.14 mmol/L (160 mg/dL) during the trial, cholestyramine was administered in an open-label fashion.

Participants visited 1 clinic on a monthly basis for the duration of the study. At each monthly visit, clinicians measured vital signs and weight, counted unused study drugs, reviewed changes in medications or medical status, provided new supplies of study drugs, and sampled fasting blood. We obtained full lipid profiles (including measured LDL cholesterol level), liver enzyme levels, and fasting blood glucose level monthly for the first 6 months and then bimonthly for the remainder of the study. We performed a directed interview, cardiovascular review of systems, and physical examination at 3-month intervals.

At the baseline catheterization, we obtained 5 views of the left coronary artery and 3 views of the right coronary artery. These views gave at least 1 clear look at each coronary segment and formed 4 pairs of perpendicular views that were suitable for biplane quantitative analysis. We recorded the use of nitrates and other vasoactive drugs and the sequence of arteriographic projections, x-ray field, and catheter size. These conditions were duplicated at the follow-up catheterization 30 months later.

Change in the severity of coronary disease was assessed quantitatively in the core laboratory of one of the authors. The techniques used to assess luminal stenosis in this laboratory have been previously described (12, 14). In assessment angiograms at baseline and follow-up, 2 experienced observers were blinded to the patients' identity and treatment group and to the sequence of films. Each of the 2 films, which were obtained 30 months apart, had its leader cut off and was labeled only with a study code. The observers viewed the pairs of films simultaneously side by side at 5-fold magnification in a dual overhead projector system (Vanguard Instrument Corp., Melville, New York). A reference frame was marked so that specific frames could be located and a detailed coronary map was drawn to locate each lesion that had at least 20% stenosis.

Technicians selected 2 cine frames taken at the same point in the cardiac cycle as good-quality, representative images of each lesion. Whenever possible, they chose 2 frames from each of 2 perpendicular views of the lesion. On the basis of direct visual comparison, technicians classified lesions by consensus as "unchanged" or "possibly

changed." For "possibly changed" lesions, a third frame was selected for each view from each film. They designated the lesion causing the worst stenosis in each of the 9 proximal segments as the proximal lesion for that segment. If no lesions could be identified in a given proximal segment, they measured a length of "normal" vessel. They also measured other less severe lesions in these 9 segments and lesions in the more distal branches. They excluded lesions at the catheter tip from analysis.

Technicians manually traced the borders of each lesion and the catheter from the selected frames onto a standard form. For lesions classified as "unchanged" or "definitely changed," 2 selected frames were traced for each view. For "possibly changed" lesions, 3 frames were traced for each view, each by 2 technicians. An experienced technician reviewed all tracings for accuracy, and the tracings were then digitized and processed by using techniques that were developed and validated in the core laboratory. For each of the 9 coronary segments with at least 20% stenosis, we measured the diameter (in mm) at the point of greatest local narrowing (minimal diameter), with the catheter used as a scaling factor. We then measured the diameters of at least 2 normal proximal segments in similar fashion and averaged them to obtain the normal diameter for that coronary segment. We calculated the mean percentage of stenosis for each segment by using the following equation: percentage of stenosis = $100 \times (1 - \text{minimal diameter} / \text{normal diameter})$.

To obtain 1 measure of global coronary atherosclerosis for each patient, we averaged the percentage of stenosis in each diseased segment (minimum of 1 to maximum of 9). This allowed for a simple assessment of effect of the clinical intervention.

When study patients developed symptoms suggestive of an acute coronary syndrome, they were referred to our emergency department and were evaluated by physicians who were not involved in the investigation. Major adverse events were defined as hospitalization for angina, myocardial infarction, angioplasty, or coronary artery bypass surgery; stroke or transient ischemic event; and death. We collected data on these events by using a standardized questionnaire, and an independent, blinded end point committee adjudicated all serious events (deaths, myocardial infarction, and stroke or transient ischemic events). Each patient contributed only 1 event to the total of major adverse events in each treatment group.

Statistical Analysis

The primary outcome was the percentage change in global angiographic stenosis from baseline to the end of the treatment period. Secondary outcomes included a combined clinical end point of hospitalization for angina, myocardial infarction, transient ischemic attack and stroke, percutaneous intervention, coronary bypass, or death, as well as the individual components of this outcome. We also intended to compare body weight, body mass index (BMI),

Table 1. Baseline Data of Patients Randomly Assigned in the Armed Forces Regression Study*

Characteristic	Drug Therapy Group (n = 71)	Placebo Group (n = 72)
Age, y	63.3 ± 7.5	63.1 ± 6.8
Women, %	9.9	5.6
History of hypertension, %	71.8	70.8
History of angina, %	64.8	65.3
History of myocardial infarction, %	45.1	41.7
Previous smoker, %	85.9	83.3
Active smoker, %	7.0	9.7
Weight, lb	180.2 ± 28.3	185.6 ± 27.8
Body mass index, kg/m ²	26.3 ± 3.4	26.7 ± 4.0
Systolic blood pressure, mm Hg	139.0 ± 17.8	138.9 ± 17.0
Diastolic blood pressure, mm Hg	75.3 ± 9.8	76.3 ± 9.4
Medications, %		
Aspirin	88.7	90.3
β-Blocker	32.4	36.1
Calcium-channel blocker	49.3	51.4
Nitrates	33.8	29.2
Fasting blood glucose level, mmol/L (mg/dL)	2.1 ± 0.3 (81.3 ± 13.1)	2.1 ± 0.4 (82.3 ± 14.2)
Total cholesterol level, mmol/L (mg/dL)	5.0 ± 0.9 (194.2 ± 34)	5.1 ± 0.7 (198.1 ± 26.9)
LDL cholesterol level, mmol/L (mg/dL)	3.3 ± 0.7 (126.1 ± 28.7)	3.4 ± 0.6 (130.5 ± 24.0)
HDL cholesterol level, mmol/L (mg/dL)	0.9 ± 0.2 (34.1 ± 6.1)	0.9 ± 0.1 (34 ± 5.4)
Triglyceride level, mmol/L (mg/dL)	1.9 ± 0.9 (168.5 ± 81.5)	1.9 ± 0.9 (168.0 ± 81.1)
ALT level, U/L	25.2 ± 39.1	19.9 ± 10.5
Fibrinogen level, U/L	289.1 ± 67.6	288.5 ± 69.3

* Values expressed with a plus/minus sign are means ± 1 SD. ALT = alanine aminotransferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

systolic blood pressure, diastolic blood pressure, fasting blood glucose level, HDL cholesterol level, LDL cholesterol level, total cholesterol level, triglyceride level, and alanine aminotransferase level during active therapy. We collected 3-day diet histories, including calorie and dietary component counts, by using the Nutrition Data System for Research (NDS-R) software (Nutrition Coordinating Center, University of Minnesota, Minneapolis, Minnesota) at baseline, 1 year, and the end of the study.

We estimated that 110 patients (55 per group) were required, assuming a 2-sided type I error of 5%, for the study to have 80% power to detect a 2% difference in angiographic stenosis between the control group and the treatment group. This 2% progression in angiographic stenosis has been previously reported with standard medical care in angiographic studies spanning the same length of time (14).

We compiled and analyzed data by using SAS software (SAS Institute, Inc., Cary, North Carolina). We compared continuous variables by using 2-sample *t*-tests on mean percentage changes from baseline to follow-up. We compared dichotomous outcomes by using the Pearson chi-square test or the Fisher exact test when appropriate. We performed event-free survival analysis by using a proportional hazards model. For patients who experienced an event, we defined event time as the time (in months) from enrollment to the first event. We censored event time at the end of follow-up for those who did not experience an event. We used an intention-to-treat analysis for angiographic stenosis data.

Data are presented as the mean (±SD) with 95% CIs for continuous variables and as number (percentage) for

dichotomous variables. We considered a *P* value of 0.05 or less to be statistically significant.

Role of the Funding Source

A grant from the Parke Davis branch of Pfizer Pharmaceuticals funded this study. The sponsor had no role in the collection, analysis, or interpretation of the data or in the decision to submit the study for publication. The authors had full access to the study data.

RESULTS

Patient Characteristics

Table 1 provides the baseline information of the 143 patients randomly assigned in AFREGS between January 1993 and March 1994. Follow-up was completed in June 1996. Seventy-one patients received the combination of gemfibrozil and niacin with or without cholestyramine, and 72 received corresponding placebos. Patients' lipid profiles, fasting blood glucose levels, and blood pressure were well balanced between groups. All but 2 patients in each group tolerated the goal dosage of 600 mg of gemfibrozil per day (or matching placebo). The mean daily dose of niacin (±SD) achieved in the treatment group was 2.5 ± 1.0 g, while the mean daily dose of cholestyramine (±SD) was 8.4 ± 6.2 g. Seventeen patients in the placebo group and 2 in the treatment group received open-label cholestyramine (*P* < 0.001). No patients in either group crossed over to niacin or gemfibrozil, and no study patient used statins.

Adherence to Lifestyle Modification

We assessed adherence to the AHA step II diet by using 3-day diet histories at study initiation, after 50 weeks

Table 2. Measures of Adherence to American Heart Association Step 2 Diet during the Armed Forces Regression Study*

Measure	Time	Drug Therapy	Placebo	P Value
Calories	Baseline	1536.8 ± 484.4	1553.7 ± 372.8	>0.2
	50 wk	1502.3 ± 449.0	1612.8 ± 453.8	0.17
Cholesterol, μmol (mg)	Baseline	375.7 ± 233.8 (145.3 ± 90.4)	370.3 ± 190.8 (143.2 ± 73.8)	>0.2
	50 wk	410.4 ± 210.0 (158.7 ± 81.2)	393.3 ± 212.6 (152.1 ± 82.2)	>0.2
Fat, %	Baseline	37.8 ± 17.9	38.1 ± 20.8	>0.2
	50 wk	34.8 ± 15.6	37.8 ± 15.6	>0.2
Saturated fat, %	Baseline	6.7 ± 2.7	7.0 ± 3.1	>0.2
	50 wk	6.1 ± 2.4	6.7 ± 2.5	0.2

* Values expressed with a plus/minus sign are means ± 1 SD.

of drug or placebo therapy, and at the completion of the study. The diet histories showed remarkable adherence to the imposed dietary and caloric restrictions, and the 2 groups did not differ over the course of the study. **Table 2** shows the comparisons of dietary variables at study initiation and after 50 weeks of therapy.

Response to Therapy

Table 3 compares the changes in weight, blood pressure, and blood work in the 2 groups after 50 weeks of therapy and changes in angiographic stenosis between the baseline and follow-up catheterization at 30 months. In the treatment group compared with the placebo group at 50 weeks, levels of total cholesterol, LDL cholesterol, and triglycerides decreased substantially, and HDL cholesterol levels increased. Similar findings for each of these characteristics were also present at 18 months and 30 months (data not shown), but data collection was less complete than at 50 weeks because of attrition due to interval clinical events. Both groups lost weight and had a decrease in BMI (data not shown), although the changes were greater in the treatment group. Fasting blood glucose level increased in the treatment group, but this did not translate to more diagnoses of diabetes according to the widely accepted fasting glucose threshold of 7 mmol/L (126 mg/dL).

Quantitative Coronary Angiography

Of the patients who were initially randomly assigned to treatment, 90% (66 patients in the treatment group and

62 controls) underwent coronary angiography at the completion of the study. Five patients in the treatment group and 10 controls did not complete the trial or declined final angiography. The demographic characteristics of the treatment and placebo groups remained similar. The mean percentage of global stenosis (\pm SD) increased from $53.4\% \pm 7.3\%$ to $54.8\% \pm 7.1\%$ in the placebo group and decreased from $54.5\% \pm 6.8\%$ to $53.7\% \pm 5.9\%$ in the treatment group, a difference of -2.1 percentage points (CI, -4.2 to -0.1 percentage points) in favor of pharmacologic therapy. The significant group comparison on change in angiographic stenosis remained statistically significant after we assigned no change to each of the 15 patients who did not complete the trial. After this assignment, the mean change in the treated group was -0.75 percentage point and the mean change in the placebo group was 1.16 percentage points (mean difference, -1.91 percentage points [CI, -3.76 to -0.06 percentage points]; $P = 0.04$).

Patients were also qualitatively categorized as having worsened, unchanged, or improved focal coronary stenosis. In the treated group, 33 patients improved, 13 were unchanged, and 20 worsened. In the control group, 26 improved, 5 were unchanged, and 31 worsened. If we assume that atherosclerosis is controlled when coronary stenosis improves or does not change, then 46 of 66 patients in the

Table 3. Changes in Stenosis and Laboratory Measures in Patients Randomly Assigned in the Armed Forces Regression Study*

Variable	Change in Drug Therapy Group, %†	Change in Placebo Group, %†	Difference (95% CI), percentage points	P Value
Angiographic stenosis‡	-0.81	1.35	-2.16 (-4.23 to -0.09)	0.04
Weight	-4.8	-0.8	-4.0 (-5.4 to -2.5)	<0.001
Systolic blood pressure	-9.8	-6.6	-3.2 (-7.4 to 1.1)	0.14
Diastolic blood pressure	6.8	4.3	2.5 (-1.7 to 6.7)	>0.2
Fasting glucose level	17.6	8.1	9.5 (2.8 to 16.1)	0.006
Total cholesterol level	-16.7	2.8	-19.6 (-24.3 to -14.8)	<0.001
LDL cholesterol level	-21.8	4.6	-26.4 (-33.7 to -19.1)	<0.001
HDL cholesterol level	37.9	2.0	35.9 (28.4 to 43.5)	<0.001
Triglyceride level	-45.6	4.2	-49.8 (-59.2 to -40.5)	<0.001
ALT level	-11.1	6.8	-17.9 (-35.1 to -0.6)	0.04
Fibrinogen level	16.34	13.7	2.65 (-8.1 to 13.4)	>0.2

* ALT = alanine aminotransferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

† Calculated as: $100 \times (\text{value at 50 weeks} - \text{value at baseline}) / (\text{value at baseline})$.

‡ Change in stenosis compares measured stenosis at catheterization at completion of study with stenosis at initial catheterization.

Table 4. Clinical Events in Patients Randomly Assigned in the Armed Forces Regression Study*

Clinical Event	Drug Therapy Group, n (%)	Placebo Group, n (%)	Difference (95% CI), percentage point†	P Value
Death	1 (1.4)	2 (2.8)	1.4 (−7.5 to 12.5)	>0.2
Hospitalization for angina	7 (9.9)	15 (20.8)	11.0 (−2.8 to 26.8)	0.14
Cerebrovascular event or TIA	0 (0)	2 (2.8)	2.8 (−5.2 to 13.5)	>0.2
PCI	2 (2.8)	5 (6.9)	4.1 (−6.2 to 16.9)	>0.2
CABG	2 (2.8)	8 (11.1)	8.3 (−2.7 to 22.0)	0.2
PCI or CABG	4 (5.6)	12 (16.7)	11.0 (−1.5 to 26.0)	0.11
Combined cardiovascular events	9 (12.7)	19 (26.4)	13.7 (0.9 to 26.5)	0.04

* CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

† Placebo − drug therapy.

treated group (70%) were controlled, compared with 31 of 62 patients in the control group (50%) ($P = 0.03$).

Clinical Events

Twenty-eight patients (19.6%) sustained a major cardiovascular end point during the follow-up period, including 9 patients (12.7%) receiving the combination drug regimen and 19 patients (26.4%) receiving placebo (difference, 13.7 percentage points [CI, 0.9 to 26.5 percentage points]; $P = 0.04$). Table 4 compares the individual components of the composite end point. Figure 2 illustrates event-free survival in both the drug and placebo groups. No ST-segment elevation myocardial infarctions occurred in either group. Of the 3 reported deaths—1 due to progression of previously diagnosed idiopathic pulmonary fibrosis, 1 due to complications during elective abdominal surgery, and 1 due to postoperative complications 1 month after coronary artery bypass grafting—only the last (which occurred in the placebo group) could be considered cardiac-related.

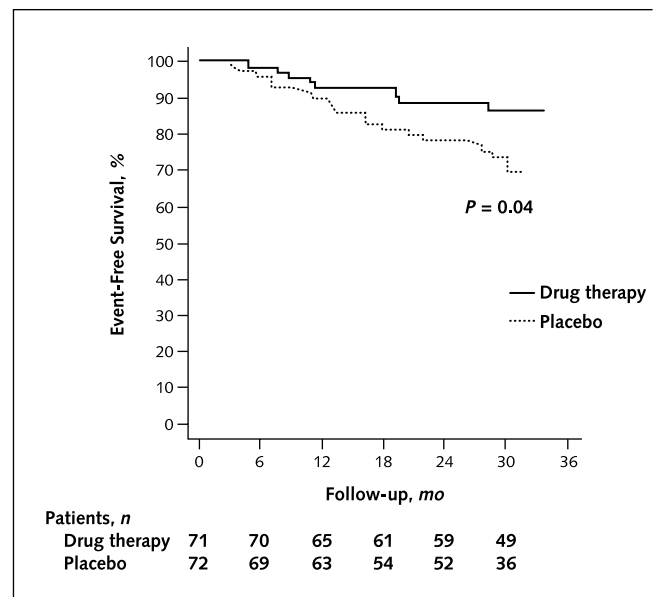
Treatment Tolerability

Drug therapy was reasonably tolerated overall. Only 7% of patients in the drug therapy group and 10% in the placebo group withdrew from the study. Adherence to the study medications, measured by pill counts at each visit, was excellent throughout the study, ranging from 87% to 90% in the drug treatment group and from 88% to 92% in the placebo group. Flushing was almost universally seen in the drug group, and 7 patients could not tolerate any dose of niacin by the completion of the study (compared with 2 patients in the placebo group). Skin rashes were the next most common complication in the treatment group (Table 5). Gastrointestinal symptoms were also cumulatively more common in the treatment group (22 patients compared with 10 patients in the placebo group; $P = 0.014$). Three splenic ruptures occurred during colonoscopy to evaluate heme-positive stools, all of which occurred in the treatment group. Three different operators performed colonoscopies in 2 different clinics, and no common cause for these perforations was discovered.

DISCUSSION

The Armed Forces Regression Study demonstrates that a strategy aimed at increasing HDL cholesterol levels in patients with low baseline LDL cholesterol levels and established coronary disease arrests angiographic progression and might reduce the rate of some cardiovascular events. Furthermore, this strategy is beneficial when patients are already subjected to aggressive lifestyle modification. The latter strategy resulted in a significant loss of weight in the entire cohort and dramatically reduced overall cardiovascular risk. In fact, no patient experienced a myocardial infarction over the 30-month follow-up period, and only 1 death in the placebo group could be attributed to cardiovascular disease, even though all patients were considered high risk (documented, obstructive coronary artery disease) at the

Figure 2. Kaplan–Meier event-free survival curves for patients in the control and treatment groups of the Armed Forces Regression Study.



Defined clinical events included hospitalization for angina, myocardial infarction, transient ischemic attack and stroke, percutaneous intervention, coronary bypass, or death. The composite clinical end point decreased 52% after 30 months of follow-up ($P = 0.039$).

Table 5. Reported Adverse Effects in Patients Randomly Assigned in the Armed Forces Regression Study

Adverse Effect	Drug Therapy Group, n (%)	Placebo Group, n (%)	Difference (95% CI), percentage points*	P Value
Newly diagnosed diabetes	1 (1.4)	1 (1.4)	0 (−9.6 to 9.4)	>0.2
New borderline diabetic	10 (14.1)	5 (6.9)	−7.1 (−21.1 to 6.3)	>0.2
Flushing	65 (91.6)	18 (25)	−66.6 (−78.5 to −54.6)	<0.001
Skin rash	29 (40.9)	5 (6.9)	−33.9 (−46.8 to −21.1)	<0.001
Skin cancer	10 (14.1)	5 (6.9)	−7.1 (−17.1 to 2.9)	0.16
Abdominal pain	14 (19.7)	8 (11.1)	−8.6 (−20.4 to 3.2)	0.15
Cholelithiasis	4 (5.6)	1 (1.4)	−4.2 (−15.5 to 6.1)	>0.2
Gastrointestinal bleeding	4 (5.6)	1 (1.4)	−4.2 (−15.5 to 6.1)	>0.2
Fatigue	8 (11.3)	7 (9.7)	−1.5 (−11.6 to 8.5)	>0.2
Sexual dysfunction	3 (4.2)	3 (4.2)	0 (−11.5 to 11.1)	>0.2
Need for additional antihypertensive therapy	18 (25.4)	24 (33.3)	8.0 (−6.9 to 22.9)	>0.2

* Placebo − drug therapy.

time of randomization. The timing of the study (initiated before the advent of statin mortality data and aggressive LDL cholesterol goals) permitted the observation of clinical effects with less confounding from the now well-established benefits of statins. The small sample size, powered toward an angiographic outcome, limits the ability to assess clinical outcomes. However, despite inclusion of so-called soft end points (transient ischemic attack and angina requiring hospitalization) in the composite clinical end point, we observed a tendency toward reduced need for revascularization with the combination drug therapy, thus reinforcing the relevance of the angiographic findings.

When combinations of drugs are used for dyslipidemia, side effects and toxicities may occur. In previous studies, monotherapy with fibrates (13, 22) and combination drug therapy with bile acid binders and niacin (14), statins and bile acid binders (14), and statins and niacin (12) were shown to be well-tolerated and to have a profound effect on cardiovascular events, as well as coronary stenosis determined by quantitative coronary angiography. The combination of a statin and a fibrate, on the other hand, increases the risk for muscular complications, and recent recommendations caution against widespread use (23, 24).

Previous studies confirmed the safety and efficacy of both gemfibrozil and niacin in treating patients with low HDL cholesterol levels, and the mechanisms of the 2 drugs seem complementary. Fibrates activate a nuclear transcription protein, peroxisome proliferator-activated receptor- α , resulting in increased HDL cholesterol production, stimulation of cholesterol removal from cholesterol-laden macrophages, and the increase in uptake of cholesterol from HDL cholesterol particles to the liver (25). Fibrates also influence many serum metabolic measures and may have anti-inflammatory, antioxidant, and antithrombotic benefits (26). Niacin, on the other hand, increases HDL cholesterol levels predominantly by preventing catabolism of apolipoprotein A-I (27). On the basis of previous data, we postulated that a combined regimen of gemfibrozil, niacin, and a bile acid binder (cholestyramine) would increase HDL cholesterol levels and that avoiding a statin could

prevent the well-described adverse drug reactions between fibrates and statins (23).

With the use of triple-drug therapy, HDL cholesterol level increased by 0.3 mmol/L (12.7 mg/dL) (37.5%) and LDL cholesterol level decreased by 0.8 mmol/L (29.4 mg/dL) (21.3%). The treated group experienced a statistically significant reduction in percentage of stenosis compared with the control group. Total cardiovascular events statistically significantly decreased in the treatment group, and several of the individual components of the composite cardiovascular measure also tended toward reductions, although these were not statistically significant. Very few patients died, and neither cardiovascular mortality nor myocardial infarction differed between groups.

The AFREGS patient sample differs substantially from the VA-HIT sample in its exclusion of diabetic patients. Much of the clinical benefit in VA-HIT was seen in this population. The results of AFREGS, therefore, expand the benefit of HDL cholesterol level-increasing therapy to all patients with coronary disease and low HDL cholesterol levels. When compared with placebo, the combination of niacin, gemfibrozil, and cholestyramine also led to substantial improvements in body weight, body mass index, triglyceride levels, and alanine aminotransferase levels. With statin therapy, LDL cholesterol reduction seems to be associated with a decrease in systemic inflammation as assessed by C-reactive protein levels (28, 29); niacin, gemfibrozil, and cholestyramine therapy did not have this effect (fibrinogen levels were not reduced with the pharmacologic intervention). It would be tempting to attribute reduction in body weight (4% more with drug therapy than with placebo) to the high frequency of gastrointestinal side effects, but carefully performed dietary surveys did not show any statistically significant differences in caloric intake between study groups at randomization or after 12 months of medication. This finding, therefore, remains unexplained and would benefit from further study.

A statistically significant increase in the mean fasting blood glucose level was seen in the drug group (as expected when higher doses of niacin are used) (30), but this did not

lead to an increase in the diagnosis of diabetes. The medications did lead to a greater incidence of flushing, skin rashes, and abdominal symptoms, but these were generally well tolerated and rarely led to withdrawal from the protocol. When this regimen is applied to the general population, in whom follow-up will inevitably be less rigorous, adherence may be a greater limitation. Although our study used immediate-release niacin, newer formulations have since been shown to have much greater tolerability (31).

The results of AFREGS strengthen the role of HDL cholesterol level-increasing therapy in patients with coronary disease and low HDL cholesterol levels. In light of the results of the Heart Protection Study (32), which suggest that statin therapy may be beneficial in high-risk patients regardless of entry LDL cholesterol level, it provides another alternative therapeutic target. With the advent of newer, more potent agents that target HDL cholesterol, such as recombinant HDL cholesterol molecules (19) and inhibitors of cholesteryl ester transfer protein (33), AFREGS provides hope for more aggressive reduction of global cardiovascular risk that must be examined in larger trials.

From Heart and Vascular Institute of San Antonio, San Antonio, Texas, Wilford Hall Medical Center, Lackland Air Force Base, and University of Texas School of Public Health, Houston, Texas; Cardiology Consultants, Grant Pass, Oregon; Northwestern University, Chicago, Illinois; University of Washington School of Medicine, Seattle, Washington; and Weill Medical College of Cornell University, New York, New York.

Disclaimer: The opinions expressed in this article are those of the authors, not the U.S. Air Force.

Acknowledgments: The authors thank Jennifer Palmer for her assistance with editing the manuscript.

Grant Support: By an unrestricted grant from the Parke Davis Branch of Pfizer Pharmaceuticals.

Potential Financial Conflicts of Interest: *Consultancies:* R.A. Krasuski (Pfizer Pharmaceuticals), A.M. Gotto Jr. (Pfizer Pharmaceuticals); *Honoraria:* R.A. Krasuski (Pfizer Pharmaceuticals), A.M. Gotto Jr. (Pfizer Pharmaceuticals, Kos Pharmaceuticals); *Grants received:* R.A. Krasuski (Pfizer Pharmaceuticals).

Requests for Single Reprints: Richard A. Krasuski, MD, U.S. Air Force Medical Center, 759 MSGS/MCCC, 2200 Bergquist Drive, Suite 1, Wilford Hall Medical Center, Lackland Air Force Base, TX; e-mail, Richard.krasuski@lackland.af.mil.

Current author addresses and author contributions are available at www.annals.org.

References

1. Assmann G, Schulte H, von Eckardstein A, Huang Y. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. *Atherosclerosis*. 1996;124 Suppl:S11-20. [PMID: 8831911]
2. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High

density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *Am J Med*. 1977;62:707-14. [PMID: 193398]

3. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA*. 1984;251:351-64. [PMID: 6361299]

4. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335:1001-9. [PMID: 8801446]

5. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333:1301-7. [PMID: 7566020]

6. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-9. [PMID: 7968073]

7. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med*. 1998;339:1349-57. [PMID: 9841303]

8. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986;8:1245-55. [PMID: 3782631]

9. Manninen V, Elo MO, Frick MH, Haapa K, Heinonen OP, Heinsalmi P, et al. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA*. 1988;260:641-51. [PMID: 3164788]

10. Goldenberg I, Goldbourt U, Boyco V, Behar S, Reicher-Reiss H. On-treatment increments in serum high-density lipoprotein levels are associated with improved survival in patients with coronary heart disease: an extended follow-up of the Bezafibrate Infraction Prevention Trial [Abstract]. *J Am Coll Cardiol*. 2003;41:316A.

11. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med*. 1999;341:410-8. [PMID: 10438259]

12. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345:1583-92. [PMID: 11757504]

13. Ericsson CG, Hamsten A, Nilsson J, Grip L, Svane B, de Faire U. Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male postinfarction patients. *Lancet*. 1996;347:849-53. [PMID: 8622389]

14. Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med*. 1990;323:1289-98. [PMID: 2215615]

15. Blankenhorn DH, Azen SP, Krams DM, Mack WJ, Cashin-Hemphill L, Hodis HN, et al. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). The MARS Research Group. *Ann Intern Med*. 1993;119:969-76. [PMID: 8214993]

16. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). *Lancet*. 1994;344:633-8. [PMID: 7864934]

17. Waters D, Higginson L, Gladstone P, Kimball B, Le May M, Boccuzzi SJ, et al. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. *Circulation*. 1994;89:959-68. [PMID: 8124836]

18. Jukema JW, Bruschke AV, van Boven AJ, Reiber JH, Bal ET, Zwinderman AH, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation*. 1995;91:2528-40. [PMID: 7743614]

19. Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA*. 2003;290:2292-300. [PMID: 14600188]

20. Whitney EJ, Ashcom TL, Hantman RK, Heironimus J. Reversibility of fixed atherosclerotic lesions with aggressive risk factor modification. *Mil Med.* 1991;156:422-9. [PMID: 1956536]
21. Pasternak RC, Brown LE, Stone PH, Silverman DI, Gibson CM, Sacks FM. Effect of combination therapy with lipid-reducing drugs in patients with coronary heart disease and "normal" cholesterol levels. A randomized, placebo-controlled trial. Harvard Atherosclerosis Reversibility Project (HARP) Study Group. *Ann Intern Med.* 1996;125:529-40. [PMID: 8815751]
22. Frick MH, Syvanne M, Nieminen MS, Kauma H, Majahalme S, Virtanen V, et al. Prevention of the angiographic progression of coronary and vein-graft atherosclerosis by gemfibrozil after coronary bypass surgery in men with low levels of HDL cholesterol. Lipid Coronary Angiography Trial (LOCAT) Study Group. *Circulation.* 1997;96:2137-43. [PMID: 9337181]
23. Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol.* 2002;40:567-72. [PMID: 12142128]
24. Xydakis AM, Ballantyne CM. Combination therapy for combined dyslipidemia. *Am J Cardiol.* 2002;90:21K-29K. [PMID: 12467937]
25. Fruchart JC, Staels B, Duriez P. The role of fibric acids in atherosclerosis. *Curr Atheroscler Rep.* 2001;3:83-92. [PMID: 11123853]
26. Elisaf M. Effects of fibrates on serum metabolic parameters. *Curr Med Res Opin.* 2002;18:269-76. [PMID: 12240789]
27. Kamanna VS, Kashyap ML. Mechanism of action of niacin on lipoprotein metabolism. *Curr Atheroscler Rep.* 2000;2:36-46. [PMID: 11122723]
28. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation.* 2004;109:II2-10. [PMID: 15173056]
29. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA.* 2001;286:64-70. [PMID: 11434828]
30. Grundy SM, Vega GL, McGovern ME, Tulloch BR, Kendall DM, Fitz-Patrick D, et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. *Arch Intern Med.* 2002;162:1568-76. [PMID: 12123399]
31. Knopp RH. Evaluating niacin in its various forms. *Am J Cardiol.* 2000;86:51L-56L. [PMID: 11374857]
32. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360:7-22. [PMID: 12114036]
33. Brousseau ME, Schaefer EJ, Wolfe ML, Bloedon LT, Digenio AG, Clark RW, et al. Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol. *N Engl J Med.* 2004;350:1505-15. [PMID: 15071125]

Current Author Addresses: Dr. Whitney: Heart and Vascular Institute of Texas, 1933 NE Loop 410, San Antonio, TX 78217.

Drs. Krasuski, Maranian, and Kolasa: 759 MSGS/MCCC, 2200 Bergquist Drive, Suite 1, Wilford Hall Medical Center, Lackland Air Force Base, TX 78236-5300.

Dr. Personius: Cardiology Consultants, 520 SW Ramsey Avenue, Suite 101, Grants Pass, OR 97526.

Dr. Michalek: University of Texas School of Public Health, 5323 Harry Hines Boulevard, V8.112M, Dallas, TX 75390-9128.

Dr. Monick: Department of Medicine, Northwestern University—The Feinberg School of Medicine, 251 East Huron Street, Galter Pavilion, Suite 3-150, Chicago, IL 60611.

Dr. Brown: Box 356422, University of Washington, 1959 NE Pacific Street, Seattle, WA 98195-6422.

Dr. Gotto: Joan and Samuel Weill College of Medicine, Cornell University, 1300 New York Avenue, Box 5, New York, NY 10021.

Author Contributions: Conception and design: E.J. Whitney, B.G. Brown.

Analysis and interpretation of the data: E.J. Whitney, R.A. Krasuski, B.E. Personius, A.M. Maranian, M.W. Kolasa, E. Monick, B.G. Brown.

Drafting of the article: E.J. Whitney, R.A. Krasuski, B.E. Personius.

Critical revision of the article for important intellectual content: E.J. Whitney, R.A. Krasuski, B.E. Personius, A.M. Maranian, E. Monick, B.G. Brown, A.M. Gotto Jr.

Final approval of the article: E.J. Whitney, R.A. Krasuski, B.G. Brown, A.M. Gotto Jr.

Provision of study materials or patients: E.J. Whitney.

Statistical expertise: E.J. Whitney, R.A. Krasuski, J.E. Michalek.

Obtaining of funding: E.J. Whitney.

Administrative, technical, or logistic support: E.J. Whitney, R.A. Krasuski, A.M. Maranian.

Collection and assembly of data: E.J. Whitney, R.A. Krasuski, A.M. Maranian, M.W. Kolasa, E. Monick.