

Design & Rationale of the Air Force/ Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

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The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) is a randomized, double-blind, placebo-controlled primary prevention trial. It is designed to test the hypothesis that in addition to a lipid-lowering diet, treatment with lovastatin is more effective than placebo in reducing acute major coronary events (i.e., sudden cardiac death, fatal and nonfatal myocardial infarction, and unstable angina) in a cohort with normal to mildly elevated total (180 to 264 mg/dl) and low-density lipoprotein (LDL) cholesterol (130 to 190 mg/dl) and low high-density lipoprotein (HDL) cholesterol (≤ 45 mg/dl for men and ≤ 47 mg/dl for women). Two sites in Texas, Lackland Air Force Base in San Antonio and the University of North Texas Health Science Center in Fort Worth, will conduct the study. After at least 12 weeks of an American Heart Association Step 1 diet and 2 weeks placebo run-in, 6,605 men and women, ages 45 to 73 and 55 to 73 years, respectively, without clinical evidence of coronary heart disease, are randomized in equal numbers to either lovastatin (20 mg/day) or placebo. Study procedures maintain the blind, allowing titration of lovastatin from 20 to 40 mg/day to achieve an LDL cholesterol goal of ≤ 110 mg/dl. All par-

ticipants are followed until study completion, when 320 participants have had a primary end point or a minimum of 5 years after the last participant is randomized, whichever occurs last. All end points are adjudicated by an independent committee using prespecified criteria. Unique features of this trial are (1) the inclusion of unstable angina in the primary end point to reflect the increasing trend to treat coronary heart disease aggressively before a myocardial infarction has occurred, (2) aggressive pharmacologic intervention, with titration, to attain an LDL cholesterol goal less than the current National Cholesterol Education Panel guidelines for primary prevention, and (3) a cohort that includes women, the elderly, and those with mild to moderate hyperlipidemia and low HDL cholesterol. Compared with earlier studies, results will be applicable to a broader population and may help clarify the role of aggressive LDL cholesterol reduction measures in primary prevention. Treatment of this population is likely to realize the greatest cumulative long-term benefit in the prevention of acute major coronary events. © 1997 by Excerpta Medica, Inc.

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For large segments of the U.S. population at increased risk of coronary heart disease (CHD), specifically, those with total cholesterol >240 mg/dl, low high-density lipoprotein (HDL) cholesterol and the elderly, the effect of risk factor modification with aggressive low-density lipoprotein (LDL) cholesterol reduction remains unknown. The relation between plasma cholesterol concentration and CHD mortality rate is continuous, graded, and strong, with no evidence of a threshold effect at either limit.¹⁻³ Most coronary events occur in persons who do not have high total cholesterol. In the Multiple Risk Factor Intervention trial, most events occurred in participants with a total cholesterol of 182 to 264 mg/dl,⁴ and in the Framingham Heart Study, 40% of partic-

ipants who developed myocardial infarction had a total cholesterol of 200 to 250 mg/dl.^{2,5} These data suggest that there may be benefit in lipid lowering as a primary prevention intervention in cohorts with total cholesterol levels lower than those previously studied.³ Exploring the effects of risk reduction in these segments is an important consideration in the design of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). This study tests the hypothesis that, in addition to lipid-lowering diet, treatment with lovastatin will significantly reduce the risk of fatal and nonfatal acute major coronary events compared with placebo.

Study design: AFCAPS/TexCAPS is a double-blind, randomized, placebo-controlled trial designed and powered to investigate whether chronic lipid lowering with diet and lovastatin will decrease the rate of first acute major coronary events (i.e., sudden cardiac death, fatal and nonfatal myocardial infarction, and unstable angina) compared to intervention with diet alone during at least 5 years of follow-up in a cohort without clinical evidence of atherosclerotic cardiovascular disease and with normal to mildly elevated total and LDL cholesterol and low

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HDL cholesterol. Secondary objectives are to investigate whether chronic treatment with lovastatin, compared with placebo, will decrease cardiovascular morbidity and mortality across the spectrum of clinical events, by measuring the rates of: (1) fatal and nonfatal coronary revascularization procedures, (2) unstable angina, (3) fatal and nonfatal myocardial infarction, (4) fatal and nonfatal cardiovascular events, (5) fatal and nonfatal coronary events, (6) cardiovascular mortality, and (7) CHD mortality. Tertiary objectives are to provide further support of the long-term safety of lovastatin therapy, specifically, to investigate whether chronic treatment with lovastatin, compared with placebo, will result in similar rates of: (1) total mortality, (2) noncardiovascular mortality (with subset analyses for accidental/violent death and for death from cancer), (3) fatal and nonfatal cancer (excluding basal cell and squamous cell skin cancers), and (4) discontinuation for adverse drug effects. (For summary of cardiovascular end points see Appendix 1.)

Each of the 2 clinical sites participating in the trial enroll both civilians and active or retired military personnel. The San Antonio, Texas site is located at Lackland Air Force Base and the Fort Worth site is located at the University of North Texas Health Science Center in Fort Worth, Texas. To reflect the contributions of the 2 clinics, the study acronym is AF-CAPS/TexCAPS.

All participants undergo dietitian-taught group instruction in the American Heart Association Step 1 diet commencing at least 12 weeks before randomization (week 12) and reinforced at weeks 4 and 2. Baseline observations include collection of medical history, health habit, and demographic data (see Appendixes 2 and 3 for details), physical examination, eye examination (San Antonio clinic only), chest x-ray, mammogram (women), electrocardiogram, and analysis of lipids/lipoproteins, hematology, blood chemistry, and urine. A 2-week placebo baseline run-in is followed by randomization of eligible compliant participants to treatment with either lovastatin or placebo.

Participants include 6,605 men and women with normal to mildly elevated cholesterol and reduced HDL cholesterol defined as total cholesterol 180 to 264 mg/dl, LDL cholesterol 130 to 190 mg/dl, HDL to cholesterol ≤ 45 mg/dl for men, and ≤ 47 mg/dl for women, and triglycerides ≤ 400 mg/dl. All lipid/lipoprotein entrance criteria must be met on average at both 4 and 2 weeks before randomization (after at least 8 weeks of diet therapy). In addition, for both total and LDL cholesterol, the 2 eligibility determinations must be within 15% of each other.

Excluded for clinical evidence of atherosclerotic cardiovascular disease are men and women who have prior history of myocardial infarction, angina, claudication, cerebrovascular accident, or transient ischemic attack. Also excluded are those aged >73 or <45 (men) or <55 (women) years or those with secondary hyperlipoproteinemia, nephrotic syndrome, uncontrolled or insulin-dependent diabetes

mellitus, or uncontrolled hypertension. At their discretion, investigators could also exclude those who would have difficulty completing a study of at least 5 years duration (e.g., due to compliance problems or reduced life expectancy).

Beginning May 30, 1990, and ending February 12, 1993, participants are randomized to either placebo or lovastatin 20 mg once a day, and are stratified by center and gender so that there is an equal chance of being assigned to lovastatin or placebo. Formal procedures ensure maintenance of the study blind. Participants, investigators, Steering Committee members, and those providing participant care, monitoring or managing data, or adjudicating end points are blinded. For participant safety, an independent Data and Safety Monitoring Board is not blinded (see Appendix 4 for membership). In addition, 2 programmers and the study statistician who performs analyses for the safety monitoring board have access to either the allocation schedule or the unblinded lipid value.

On the day participants are randomized and before initiation of lovastatin or placebo double-blind treatment, they receive dietary advice and are questioned about adverse experiences during the placebo run-in. In addition, lipid analysis (including apolipoprotein (Apo) A1 and Apo B), hematology, blood chemistry, and urinalysis are performed.

During the first 48 weeks of active treatment, participants return to the clinic at 6-week intervals. At each visit, participants are asked about adverse events and laboratory safety tests for liver enzymes and creatine kinase are performed. Every 12 weeks, participants also receive dietary reinforcement. During the first 6 months, a lipid profile is performed at every visit. At week 48, participants receive dietary advice and undergo an extensive evaluation that includes the tests routinely done at each visit as well as a physical examination, electrocardiogram, mammography (women), ophthalmologic examination (San Antonio clinic only), complete blood chemistry, hematology, and urinalysis.

After week 48, the interval between visits is longer (week 60, month 18, then every 6 months). At week 60 and at all "mid-year" visits, adverse experience inquiry and laboratory safety tests are performed. The year-end visit includes all tests and observations described at the week 48 visit. At week 48 and year 5, Apo A1 and B are measured. At all protocol visits, pharmacists assess compliance by pill counts.

To achieve an on-treatment LDL cholesterol of ≤ 110 mg/dl, participants are titrated to lovastatin 40 mg once a day based on LDL cholesterol values at 6 and 12 weeks after randomization. Participants in the lovastatin treatment group with LDL cholesterol >110 mg/dl at both visits are titrated at week 18 to 40 mg once a day of lovastatin by taking two 20 mg tablets once a day. To maintain the blind, an equal number of randomly selected participants in the placebo treatment group are also titrated to 2 tablets/day. If total cholesterol values are <100 mg/dl on 2

successive scheduled visits, a titrated participant's dose is decreased to 1 tablet/day. To maintain the blind, an equal number from the titrated placebo group also have their doses reduced. Participants are flagged for withdrawal by the unblinded programmer if either they have total cholesterol <100 mg/dl on repeated measurements after back titration or LDL cholesterol values >195 mg/dl on successive visits after titration. The investigator, the participant, and those involved in the participant's care are never given the participant's lipid values.

A central laboratory at Wilford Hall Medical Center, Lackland Air Force Base, Texas, analyzes fresh sera from both sites for total and HDL cholesterol and triglycerides. HDL cholesterol is isolated from LDL cholesterol and very low density lipoprotein cholesterol by Polyanion precipitation procedure using dextran sulfate (50 kDa) and magnesium chloride.⁶ LDL cholesterol is calculated by use of the Friedewald formula.⁷ Frozen sera are analyzed for apo A1 and B by a lipid specialized laboratory at Johns Hopkins. Apo A1 and B are measured by immunoephelometry (BNA-100, Behring diagnostics, Westwood, Maryland). Calibration for both assays is traceable to World Health Organization International reference material.⁸ Both central lipid laboratories maintain part II standardization from the Centers for Disease Control and the National Heart, Lung, and Blood Institute.⁹

The central laboratory at Wilford Hall Medical Center also analyzes all per-protocol blood chemistry safety tests for both sites. Hematology studies are done at the individual clinics. All laboratories are accredited by the College of American Pathologists. A laboratory committee monitors quality control data from the central laboratories (see Appendix 4 for committee membership).

The principal investigator and his designees in the clinics monitor participant safety. The investigators routinely review blinded summaries of participant adverse experiences. The principal investigator presents blinded summaries of specific clinical adverse experiences, such as liver function test abnormalities and creatine kinase elevations to both the Steering Committee and the Data and Safety Monitoring Board.

The Data and Safety Monitoring Board reviews unblinded safety data approximately twice a year. The review includes summary laboratory data, quality assurance reports, and serious adverse experiences defined as (1) requiring or prolonging hospitalization, (2) resulting in a permanent or substantial disability, (3) cancers, and (4) deaths. The Data and Safety Monitoring Board may request the advice of consultants in evaluating rates of specific serious adverse experiences. After each review, the Data and Safety Monitoring Board votes on whether to stop the study, and their recommendation is reported to the Steering Committee.

The AFCAPS and TexCAPS clinical staffs are trained to report all potential end point events for further follow-up, and ultimately, for End point

Committee (see Appendix 4 for membership) review. The clinic staff compiles packages with documentation of blinded data required to adjudicate the end point event. At no point in the collection process is there any attempt to filter cases. The End point Committee meets to review data packages for all possible end point events. Determinations require the approval of all members who follow specific definitions for adjudication of events. Definitions of primary end point events are listed in Appendix 5.

Statistical considerations: The primary hypothesis, that lovastatin will reduce the incidence of acute major coronary events, is assessed based on an intention-to-treat approach, i.e., all patients randomized are included based on their randomized treatment assignment.

Treatment group differences are assessed using the log rank test with study site and gender as stratification factors. Relative risks and 95% confidence intervals are calculated using the Cox regression model, in particular SAS PROC PHREG.¹⁰ The Cox proportional-hazards model has treatment as the model effect and study site and gender as the stratification factors. Cumulative event-free (survival) proportions and interval estimates will be calculated using the life-table method.

A secondary, exploratory analysis of the primary end point uses the Cox regression model and relevant baseline demographic and lipid factors as well as on-treatment lipids and percent change in lipids. Each factor is assessed in a univariate manner by including it in a Cox regression with the treatment groups combined. Factors that do not show a trend (i.e., $p > 0.20$) are eliminated from further consideration. All individually trending factors are assessed in a backward stepwise manner and only factors (other than treatment group) that are significant at the $p \leq 0.05$ level are included in the final model.

All patients will be followed until the last randomized patient completes 5 years of treatment or until the expected total of 320 patients with primary end point events are observed, whichever comes last. A total of 3 formal analyses (2 interim and 1 final) are performed for this study. A group sequential design with an early stopping rule, which allows for interim analyses and preserves the overall type I error probability of $\alpha = 0.05$ will be used. The study may be terminated before its scheduled end if the early stopping rule prevails and both the Data and Safety Monitoring Board and Steering Committee concur.

The analyses are scheduled with respect to the information time in terms of the fraction of patients with primary end point events. Hence, the 3 planned analyses are scheduled on the information time at $t_1 = 0.375$ (120 patients with acute major coronary events), $t_2 = 0.75$ (240 patients with acute major coronary events), and $t_3 = 1.0$ (320 patients with acute major coronary events). The group sequential boundary (2-sided, $\alpha = 0.05$) for the scheduled analyses is 2.947, 2.411, and 2.011, which correspond to p values of 0.0032, 0.0159, and 0.0443, respectively.

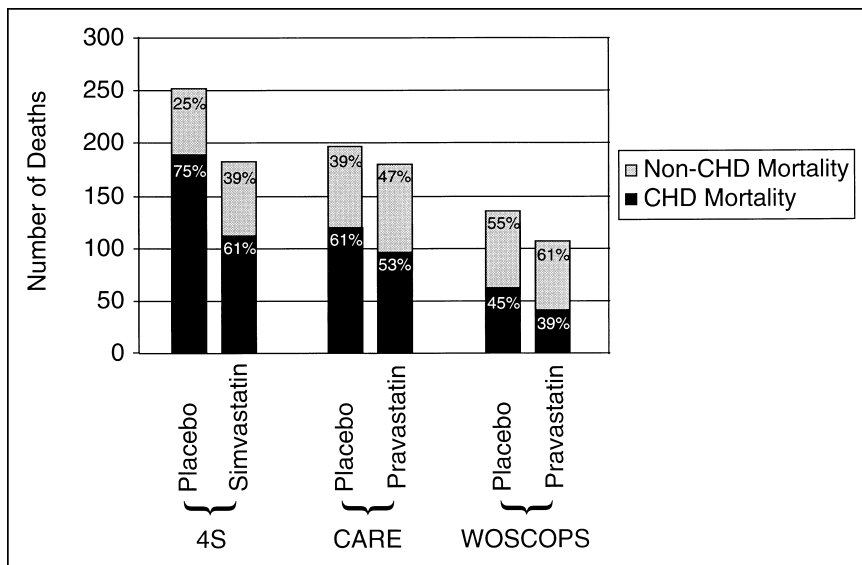


FIGURE 1. Comparison of CHD and non-CHD Mortality rates. CARE = Cholesterol and Recurrent Events trial; 4S = Scandinavian Simvastatin Survival Study; WOSCOPS = West of Scotland Coronary Prevention Study.

These boundaries are based on the 3 planned analyses and a predetermined α spending function of $\alpha(-4, t)$ which provides an O'Brien-Fleming-like boundary for unequally spaced information time.¹¹

The reduction in the primary end point due to lovastatin is hypothesized to be between 30% and 35%. The trial design for the final analysis provides 90% to 97% power, respectively, to detect such reductions in the number of patients experiencing as a first event any of the following acute major coronary events: sudden cardiac death, fatal myocardial infarction, nonfatal myocardial infarction, or unstable angina. Estimates of power were obtained using comparisons of proportions that provide more conservative estimates than those based on survival models.¹²

At the end of the study, when there are 320 patients with primary end point events, we expect approximately 110 deaths of which only 30 are likely to be due to cardiovascular causes. If there is a 30% to 35% reduction in the cardiovascular deaths due to lovastatin and no effect on the 80 noncardiovascular deaths, then one can expect approximately 52 deaths among lovastatin patients (40 noncardiovascular and 12 cardiovascular) and 58 deaths among placebo patients (40 noncardiovascular and 18 cardiovascular). The power for this comparison is quite low, approximately 7%.⁸

DISCUSSION

AFCAPS/TexCAPS is unique among primary prevention end point event trials because it includes (1) unstable angina in the primary end point, reflecting the trend to treat coronary heart disease aggressively before a myocardial infarction has occurred, (2) aggressive pharmacologic intervention, with titration, to attain an LDL cholesterol goal less than the current National Cholesterol Education Panel guidelines for primary prevention, and (3) a cohort that includes women, the elderly, and those with mild hyperlipidemia and low HDL cholesterol, mak-

ing results applicable to a broader population than prior studies.

AFCAPS/TexCAPS entrance inclusion criteria are LDL cholesterol 130 to 190 mg/dl and HDL cholesterol ≤ 45 mg/dl for men and ≤ 47 mg/dl for women. Many participants in previous primary prevention end point event trials would be excluded from AFCAPS/TexCAPS, as demonstrated by the following on-diet mean baseline LDL cholesterol and HDL cholesterol concentrations: (1) the Lipid Research Clinics Coronary Primary Prevention Trial (cholestyramine) 205 and 45 mg/dl, respectively¹³; (2) the Helsinki Heart Study (gemfibrozil), 189 and 47 mg/dl, respectively¹⁴; and (3) the West of Scotland Coronary Prevention Study (pravastatin) 192 and 44 mg/dl, respectively.¹⁵

AFCAPS/TexCAPS is specifically designed to study the effect of LDL cholesterol reduction in a cohort with normal or mildly elevated LDL cholesterol and low HDL cholesterol. National Cholesterol Education Panel guidelines for adults¹⁶ already incorporate HDL cholesterol concentration in recommendations for estimating CHD risk and selecting lipid-altering therapy. Furthermore, the LDL/HDL cholesterol ratio may be a particularly strong predictor of CHD events.¹⁷⁻¹⁹ Based on entrance criteria, it is expected that AFCAPS/TexCAPS participants will have a total/HDL cholesterol ratio ≥ 6 and a LDL/HDL cholesterol ratio ≥ 4 . Because low HDL cholesterol increases CHD risk independent of total or LDL cholesterol,^{17,18} it is important to clarify whether increasing HDL cholesterol and/or decreasing LDL cholesterol (lowering the LDL/HDL cholesterol ratio) is associated with lowering CHD risk in this high-risk primary prevention cohort. Lovastatin is expected to favorably affect LDL/HDL cholesterol and total/HDL cholesterol ratios.

The inclusion of unstable angina follows a careful review of the available literature regarding hospital discharge rates for various CHD events. The review reveals a decline in CHD incidence and associated

mortality, but an increase in hospitalization for CHD events in the U.S.^{20,21} Whereas the rate of discharge for acute myocardial infarction appears to have stabilized, the rates for unstable angina increased from 4% of CHD discharges in 1980 to 25% of CHD discharges in 1989.²² Because of these trends, unstable angina was included as a component of the primary end point in order to reflect the actual experience with CHD presentation in the U.S.

Unlike earlier studies, the secondary prevention Scandinavian Simvastatin Survival Study,²³ reported a significant decrease in total mortality rate after treatment with simvastatin (30% reduction, $p = 0.0003$). A second trial, the West of Scotland Coronary Prevention Study¹⁵ demonstrated a trend toward reduction in total mortality rate with pravastatin (22% reduction; $p = 0.051$). In both these studies, the reduction in total mortality rate was directly attributable to the significant reduction in cardiovascular deaths. AFCAPS/TexCAPS is not expected to demonstrate a significant reduction in total mortality rate because the risk of cardiovascular death is low in its study population, and lipid-lowering therapy is not thought to lower the risk of non-CHD deaths.^{24,25} (See Figure 1 for a comparison of CHD and non-CHD mortality in recent primary and secondary prevention trials).

Clinical trial data regarding lipid lowering in women and the elderly remains limited,²⁰ as are data regarding non-Caucasian populations and cohorts with multiple risk factors such as hypertension or diabetes.²⁶ In contrast to the Lipid Research Clinics Coronary Primary Prevention Trial, the Helsinki Heart Study, and the West of Scotland Coronary Prevention Study, AFCAPS/TexCAPS participants include women. It is expected that the inclusion of women, elderly, and those with diabetes, hypertension and other risk factors common in the general U.S. population will make the results of AFCAPS/TexCAPS more applicable than prior primary prevention studies. Finally, the study location may facilitate the enrollment of Hispanics, providing additional experience in this minority population. Although not powered for subgroup analyses, the effects of cholesterol lowering in subgroups such as women and the elderly will be examined. The effects of intervention in these subgroups may also be explored by a collaborative pooling project that subsumes a number of recent and ongoing trials including AFCAPS/TexCAPS.²⁷

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(Continued)

APPENDIX 1 Classification of Cardiovascular Study Events and End Points									
Events	Primary End Points*	Secondary End Points [†]							Tertiary End Point [‡] 1
		1	2	3	4	5	6	7	
Acute major coronary events (See Appendix 5 for definitions)									
Fatal									
Myocardial infarction	✓			✓	✓	✓	✓	✓	✓
Sudden death	✓				✓	✓	✓	✓	✓
Nonfatal									
Myocardial infarction	✓			✓	✓	✓			
Unstable angina pectoris	✓		✓		✓	✓			
Other events fatal									
Cardiac procedures (e.g., coronary artery bypass grafting, PTCA, coronary stenting, etc.)		✓			✓	✓	✓	✓	✓
Cerebrovascular accident					✓		✓		✓
Peripheral bypass grafting					✓		✓		✓
Congestive heart failure					✓ [§]		✓ [§]	✓ [§]	✓
Violence (trauma, suicide, homicide)									✓
Cancer									✓
Other fatal cardiovascular events that do not meet the definition of a primary end point event					✓		✓		✓
Other fatal noncardiovascular events									✓
Nonfatal									
New-onset congestive heart failure*					✓	✓			
Cardiac procedures (e.g., coronary artery bypass grafting, PTCA, coronary stenting, etc.)		✓			✓	✓			
Cerebrovascular accident: thrombotic or embolic					✓				
Transient ischemic attack					✓				
Intermittent claudication					✓				
Peripheral vascular surgery					✓				
Cerebrovascular surgery (bleeds excluded)					✓				
New-onset stable angina					✓	✓			
*Primary End Point = sudden coronary death, fatal and nonfatal myocardial infarction, and unstable angina. [†] Secondary End Points = 1 = coronary revascularization procedures; 2 = unstable angina; 3 = fatal and nonfatal myocardial infarction; 4 = fatal and nonfatal cardiovascular events; 5 = fatal and nonfatal coronary events; 6 = cardiovascular mortality; 7 = coronary heart disease mortality. [‡] Tertiary End Points = 1 = total mortality; 2 = noncardiovascular mortality. Note: All cancers and all adverse experiences will also be analyzed. [§] Coronary heart disease ischemic etiology. PTCA = percutaneous transluminal coronary angioplasty.									

APPENDIX 2 Baseline Observations	
Medical History, Health Habit, and Demographic Information	Safety Laboratory Tests
Study center	Hematology
Gender	Hemoglobin
Age	White blood cell count/differential platelets
Race	Blood chemistry
Educational level	Bilirubin (total and direct)
Military status	Alkaline phosphatase
Marital status	Aspartate aminotransferase
Weight	Alanine aminotransferase
Family history of myocardial infarction/angina	Creatinine
Smoking status and categorized amount*	Creatine kinase
Exercise status and categorized amount*	Fasting blood glucose
Alcohol use and categorized amount*	Urinalysis-dipstick analysis
Medical history/concurrent conditions (e.g., history of diabetes, hypertension, etc.)	Chemstick 9
Prior therapies	
Concomitant therapy*	
*Collected during baseline and at least annually.	

APPENDIX 3 Study Flow Chart																		
	Prestudy		Placebo Baseline		Randomization	Active/Placebo Treatment Period												
	-14	-12	-4	-2	1	6	12	18	24	30	36	42	48	60	Month	18	24	
Dietary advice		X	X	X	X		X		X		X		X					X
Physical examination				X									X					X
Ophthalmologic examination [†]				X									X					X
Chest x-ray (done only at baseline)				X														
Electrocardiogram				X									X					X
Lipids (central laboratory)*	X [†]	X	X	X	X [†]	X	X	X	X				X [†]			X		X
Laboratory safety tests			X	X [§]	X	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X	X [§]			X [§]	X
Urinalysis			X		X								X					X
Inquire for adverse effects					X	X	X	X	X	X	X	X	X	X		X		X
Mammography (women)					X								X					X

NOTE: After month 60, patients continuing in the study are seen in clinic twice each year at the half and year end visits.
*Total serum cholesterol, HDL cholesterol, triglycerides, LDL cholesterol (calculated), unless noted otherwise.
[†]Total serum cholesterol only.
[‡]Including apo A1 and apo B on frozen specimens.
[§]Liver safety and creatine kinase only.
^{||}Routine chemstick 9 analysis.
^{††}AFCAPS clinic only.

APPENDIX 4

Administration: *Steering Committee:* Antonio M. Gotto, MD, DPhil*; Peter H. Jones, MD; Jeremiah Stamler, MD; Lt. Col. John R. Downs, MD; Major Jeffrey Rothen, MD; Michael Clearfield, DO; Edwin Whitney, MD; Stephen Weis, DO; Polly A. Beere, M.D., PhD (non-voting). *Data and Safety Monitoring Committee:* John S. de Cani, PhD*; M. Stewart West, PhD; H. Alfred Tyroler, MD; Phillip D. Houck, MD (nonvoting); Donald B. Hunninghake, MD; Evan A. Stein, M.D., PhD; Deborah R. Shapiro, DPH (nonvoting). *End Point Classification Committee:* William B. Kruyer, MD*; John Farmer, MD; Steven Minor, MD. *Central Laboratory Committee:* Major Jo Haga; Joyce Gray; Glen E. Mott, PhD; Gary L. Myers, PhD; Evan Stein, MD, PhD. *Publication Committee:* Antonio M. Gotto, MD, DPhil*; Polly A. Beere, MD, PhD; Michael Clearfield, DO; John S. de Cani, PhD; Lt. Col. John R. Downs, MD; William B. Kruyer, MD; Alexandra Langendorfer (secretary); Deborah R. Shapiro, DPH; Evan Stein, M.D., PhD; Stephen Weis, DO. *Study Site Investigators:* Lt. Col. John R. Downs, MD (principal investigator, AFCAPS); Michael Clearfield, DO (co-investigator, TexCAPS); Stephen Weis, DO (co-investigator, TexCAPS).

APPENDIX 5

Primary end point events: The primary end point events include sudden cardiac death, fatal and nonfatal myocardial infarction, and unstable angina. They are defined as follows:

Fatal myocardial infarction or sudden cardiac death: The definition requires that there be no noncardiac cause of death and 1 of the following: fatal myocardial infarction-death within 28 days from the onset of

symptoms of a definite acute myocardial infarction; witnessed unexpected sudden cardiac death-within 1 hour of symptoms; death occurring >1 hour but ≤24 hours after collapse; and unwitnessed unexpected death, presumed sudden-must have confirming autopsy data or, if autopsy not performed, preceding history of CHD events or symptoms.

Nonfatal myocardial infarction: *Acute Q-Wave Myocardial Infarction*—requires definitive electrocardiogram (ECG); *Acute Non-Q-wave myocardial infarction*—definitive ECG or, if equivocal, enzymes must be diagnostic. Non-Q-wave myocardial infarction includes myocardial infarctions reperfused by either mechanical or pharmacologic means providing there is supporting ECGs and enzyme data; *Silent subclinical (remote) myocardial infarction*—definitive ECG, or, if ECG is equivocal, focal wall motion abnormality consistent with myocardial infarction on rest echo or stress thallium (fixed defect) and on catheterization, a ≥50% stenosis in a major corresponding epicardial vessel. Participants who have had a cardiac catheterization as the first diagnostic test for presumed silent (or remote) myocardial infarction are considered to have met criteria for an end point event if the catheterization findings indicate focal wall abnormalities consistent with myocardial infarction and ≥50% stenosis in a corresponding artery.

Unstable angina:* New-onset exertional and/or accelerated or rest angina and requires at least 1 of the following: stress perfusion study—≥1 mm ST-segment changes and reversible defect; 90% epicardial vessel stenosis or ≥50% stenosis in the left main artery; ≥1 mm ST-segment changes with pain on stress testing and/or resting ECG and evidence of ≥50% stenosis in a major epicardial vessel.

*Note that angina will be adjudicated as a secondary end point event if, prior to hospitalization, the participant was asymptomatic for >2 weeks or has been stable for >1 month (defined as 28 days) even if the criteria for unstable angina, noted above, are met.

*Indicates Committee Chairman.