Design and Recruitment in the United States of a Multicenter Quantitative Angiographic Trial of *Pravastatin* to Limit Atherosclerosis in the Coronary Arteries (PLAC I)

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The present study was designed to test the effect of pravastatin, a new, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, on the progression of coronary artery disease in patients with moderate hypercholesterolemia. Angiographic entry criteria included the presence of ≥1 stenosis ≥50% in a major epicardial coronary artery, and certification of film quality through the core angiography laboratory. Patients qualified for randomization if after diet stabilization their low density lipoprotein cholesterol concentrations were ≥130 and <190 mg/dl, and triglycerides were ≤350 mg/dl. Pravastatin (40 mg) or placebo is administered once daily at bedtime. Arteriography will be repeated at the end of 3 years of treatment. The primary end point of the study is the change in absolute mean coronary artery diameter. During a 30-month recruitment period, 44,145 patients were screened, and 408 were randomized. The most frequent reason for excluding patients during the screening and dietary lead-in periods was a low serum cholesterol level. A large proportion of patients with documented coronary artery disease have cholesterol concentrations that are considered to be normal or only modestly increased. Adherence to strict standards of quality control for digital analysis of angiograms ensures that baseline angiograms can be interpreted at the end of 3-year follow-up.

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Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I) is a multicenter, prospective, randomized, placebo-controlled trial of the effect of lipid-altering therapy on the progression of coronary artery disease. The study was designed with 2 goals: The first was to evaluate the effects of monotherapy with pravastatin, a hydrophilic 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, on progression and regression of coronary artery disease measured by quantitative angiography. The second goal was to evaluate progression and regression of atherosclerosis in patients with only moderate increases of low-density lipoprotein (LDL) cholesterol, typical of those with symptomatic coronary artery disease. This article describes the protocol design and recruiting experience.

METHODS

The protocol was approved by the institutional review board at each study site. All patients gave written, informed consent to participate in the trial. The study was initiated in early 1988, and randomization ended after a 30-month recruitment period. All follow-up angiography will be completed in the spring of 1993.

Screening angiography: At each site (see Appendix), all patients undergoing clinically indicated coronary arteriography were screened for eligibility. The protocol for angiography required ≥2 orthogonal or near-orthogonal views of all coronary segments, central placement of the catheter (>5Fr) in the radiographic image, administration of nitroglycerin before injection of contrast medium (in the absence of contraindications), and detailed documentation of the sequence of injections during the procedure, including the angles of view.

A patient had to have ≥1 stenosis ≥50% in a major epicardial coronary artery to qualify for the study. The protocol required review of the documentation of the procedure, presence of an adequate portion of the angiographic catheter in a central portion of the image, digitization of eligible angiographic segments, and exclusion of excessive contrast streaming. A previously described and validated quantitative coronary artery evaluation method was used to analyze all focal stenoses in any study segment.[1]

Dietary stabilization/qualification for randomization: Patients who fulfilled the initial screening criteria were referred to a dietician for instruction in a fat-restricted, low-cholesterol diet (American Heart Associa-

TABLE I Protocol Exclusion Criteria

1. Life-threatening illnesses other than coronary artery disease with expected survival <3 years
2. Premenopausal women of childbearing potential
2. Age >75 years
3. Secondary causes for increased low-density lipoprotein cholesterol
4. Diabetes mellitus (fasting blood sugar >140 mg/dl, or needing treatment with insulin or oral hypoglycemic agents)
5. Congestive heart failure with ejection fraction <30%
6. Significant hepatic disease (alanine or aspartate aminotransferase, total bilirubin or alkaline phosphatase greater than upper limit of normal)
7. Significant renal disease (creatinine >2.5 mg/dl, urinary protein >2+, and serum albumin <3 g/dl)
8. Blood pressure >160 mm Hg (systolic) or >100 mm Hg (diastolic) despite treatment, or untreated
9. History of cerebrovascular disease
10. Gastrointestinal disease or surgery that may interfere with drug absorption
11. Alcohol consumption >3 drinks/day (1 drink = 1.5 oz of 80 proof liquor, or equivalent)
12. Chronic pancreatitis
13. History of hypersensitivity to 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors
14. Systemic lupus erythematosus

tion Phase I or equivalent[2]). After ≥4 weeks of a stable diet, the first lipid profile was determined; subsequent determinations were obtained at 1- to 4-week intervals. To qualify for randomization, the average of 2 consecutive LDL cholesterol concentrations needed to be ≥130 mg/dl (3.36 mmol/liter) but <190 mg/dl (4.91 mmol/liter), and the average triglycerides ≤350 mg/dl (3.95 mmol/liter).

Other inclusion/exclusion criteria: Before enrollment in the study, patients had to consent to coronary arteriography again at the end of 3 years of treatment. Patients receiving treatment with lipid-lowering therapy could be enrolled if an appropriate drug washout period preceded the first qualifying lipid determination. Other exclusion criteria are listed in Table I.

Drug therapy and administration: Pravastatin or matching placebo (provided by the Bristol-Myers Squibb Pharmaceutical Research Institute) is administered as two 20 mg tablets at bedtime (40 mg total), and dosage remains fixed for the duration of the study unless safety considerations dictate a reduction. Assignment to placebo or active drug is balanced within strata defined by clinical characteristics (myocardial infarction, percutaneous transluminal coronary angioplasty and stable or unstable angina) and baseline LDL cholesterol concentration (130 to 169 and 170 to 189 mg/dl).

Over the course of a 3-year study, LDL cholesterol may be expected to increase to ≥190 mg/dl, approximately the 90th percentile for the United States population in some patients. Because of the demonstrated benefits of treating patients with such marked cholesterol increase,[3] care was taken to identify and treat them. If the mean of 3 consecutive LDL cholesterol levels is ≥190 mg/dl in any patient, personnel at the site are to be notified in writing to advance the diet to the American Heart Association Phase II or equivalent diet.[2] To maintain study integrity and blinding, a patient from the other treatment group matched by age, sex and upper tertile of LDL cholesterol concentration is to be chosen to change diet also. If LDL cholesterol does not decrease to <190 mg/dl after 1 month, the patient and matching subject are to be instructed to begin taking cholestyramine resin beginning with 1 packet (bid) titrated to a maximum of 6 packets/day. Patients whose levels remain ≥190 mg/dl despite addition of cholestyramine are to be administered 5 to 10 mg of open-label pravastatin (or placebo, depending on original treatment assignment). If these measures are unsuccessful, the patient is withdrawn from the study.

Evaluation of patients: Patients are to return to the clinic every 6 weeks for the first 18 months of the study for safety evaluation (liver-enzyme elevation and adverse events), and every 12 weeks thereafter. Follow-up arteriography is to be performed after 36 months, or earlier, if feasible, in the event of withdrawal from the study, or coronary artery bypass graft surgery. As each patient completes the study, the paired baseline and follow-up cineangiograms (blinded to order and patient identification) will be reviewed by an experienced angiographer who will select matching views for analysis. (The preliminary core laboratory reading will be used only for qualification of the film.)

Interim monitoring/policy advisory board: The conduct of the study is reviewed semiannually by a policy advisory board of 5 members (see Appendix) who are independent of the sponsor and trial organization.

Statistical considerations/end point analysis plans: Original sample-size calculations were based on the limited data then available on progression rates and variability from the Coronary Artery Surgery Study.[4] A total sample size of 400 subjects was deemed adequate to demonstrate a 40% treatment effect. More recent quantitative data enable more accurate sample-size estimates.[5] Assuming a decrease in mean coronary artery diameter of 0.20 mm in the placebo group, an SD of 0.34 mm, 80% power and 0.05 significance level (2-sided), the detectable treatment effect ranges between 51 and 55% for 350 and 300 patients, respectively, completing the study (allowing for withdrawals).

The primary end point of the study is the rate of progression for mean diameter averaged over the following 10 segments: left main, proximal and mid-left anterior descending, largest diagonal, proximal and distal left circumflex, largest obtuse marginal, and proximal, mid- and distal right. Any angiogram obtained ≥90 days after initiation of double-blind therapy can be included in the analysis of the primary end point. The primary analysis will be by intention-to-treat. Rates of progression will by analyzed using rank-based tests (e.g., rank-sum tests) and expressed as a slope (mm/month). (This results in the variable being weighted for time on trial.) If a final angiogram is not available in a subject because of death or myocardial infarction, a value will be imputed for that patient equal to the greatest progression rate observed in the group completing 36 months in the trial, corrected for duration of follow-up. Arteries and segments that undergo angioplasty or coronary artery bypass graft will be excluded from the study. (Patients undergoing coronary artery surgery during the study will be defined as having reached a study end point, and the angiogram before surgery will be included in the analysis.)

Several secondary angiographic and lipoprotein end point analyses are planned (Table II). Secondary clinical end points include occurrence of myocardial infarction, stroke, angioplasty and coronary artery bypass graft surgery, and total and cause-specific mortality.

RESULTS

Recruitment began in early 1988 and ended approximately 2.5 years later (Figure 1). Tables III and IV list the reasons why patients were excluded during the screening and dietary lead-in periods. The most frequent reason for excluding a patient during the early screening phase was low serum cholesterol level. In general, subjects were enrolled in the dietary stabilization phase if the screening total cholesterol level was ≥210 to 220 mg/dl, although there was considerable variation from site to site, and the threshold depended on whether a fat-restricted diet was already being followed. Based on the accumulating experience, several changes were made in the protocol and conduct of the study (including increasing the number of participating centers) to enable randomization to be completed successfully. The protocol revision having the greatest impact on enrollment was changing the lower limit required for mean LDL cholesterol from 150 to 130 mg/dl (Figure 1). This finding provides additional support for the qualitative observation that most patients with coronary artery disease have only moderate increases of total and LDL cholesterol.

Other revisions with only modest effects on recruitment included increasing the upper age limit from 70 to 75 years, and the upper limit for triglycerides from 300 to 350 mg/dl, and allowing subjects with stable or un-

TABLE II Secondary End Points

Angiographic measurements
Mean minimal diameter
Mean maximal diameter
Mean percent stenosis
Development of new lesions
Change in average severity of lesions
Average no. of lesions and new lesions/pt.
Lesion changes stratified by baseline severity
Incidence of progression, regression and mixed progression/regression, or no change
Lipoprotein and apolipoproteins
Total and low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, high-density lipoprotein$_2$, and high-density lipoprotein$_3$
Triglycerides
Apolipoproteins A-1 and B
Lipoprotein (a)

TABLE III Patients Excluded After Screening

Patients screened	44,145
Patients excluded	43,031*
Screening total cholesterol too low	11,006
Too ill	5,068
Normal coronary arteries	4,509
Diabetes mellitus	3,975
Age	3,968
Concomitant illnesses or prohibited medications	3,862
Angiography protocol not followed	3,134
No qualifying clinical or angiographic criteria	1,138
Refused to participate	1,104
Other/not specified	5,267

*Includes 1,155 patients receiving lipid-lowering drugs.

TABLE IV Reasons for Disqualification in Patients Enrolled But Not Randomized

Patients enrolled	1,114
Patients excluded	706
Low-density lipoprotein cholesterol concentration too low	240
Triglyceride concentration too high	25
Patient withdrew	166
Angiogram rejected	54
Other/not specified	221

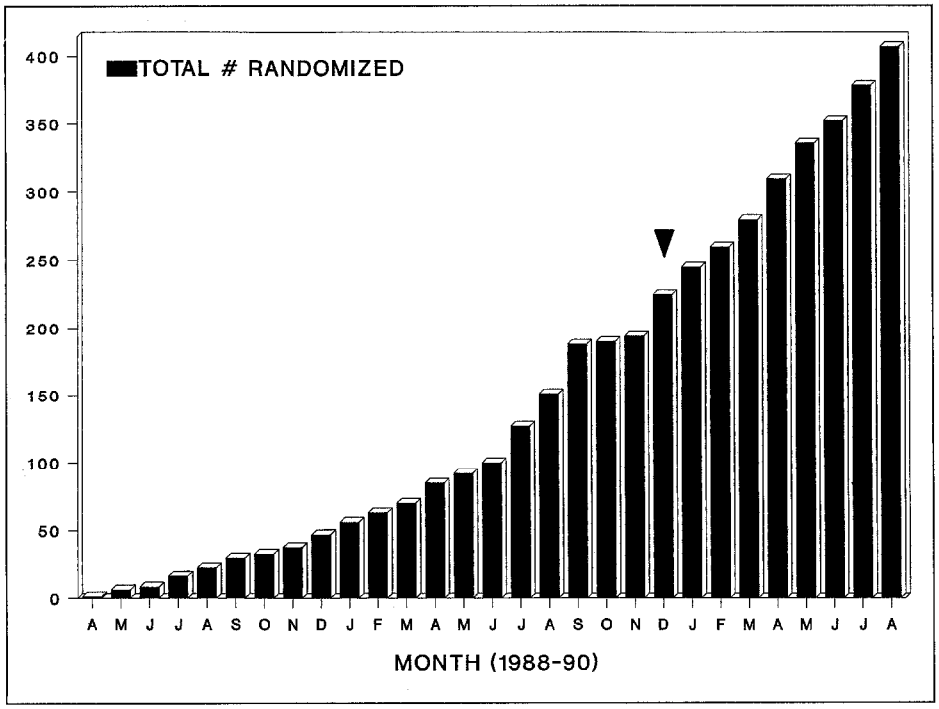

FIGURE 1. Patient recruitment. *Arrow* indicates when protocol was modified to include patients with low-density lipoprotein cholesterol ≥130 mg/dl.

TABLE V Reasons for Rejection of Baseline Angiograms by Core Angiography Laboratory

Excessive streaming	24
Excessive editing	22
No qualifying lesion	15
Absent or inadequate views	9
3-vessel bypass	8
Nitroglycerin not given	5
Inadequate documentation	4
Automated catheter tracking not possible	1
Angioplasty urgently needed	1
Total films rejected	89
Total films screened	895

stable angina (in addition to those after myocardial infarction or angioplasty) to participate in the study.

Tables III and IV show that some patients were excluded from the study because either the angiographic protocol was not followed, or qualifying clinical or angiographic criteria were absent, or both. Some patients were included whose angiograms were sent for certification, but were not accepted after analysis in the core angiography laboratory. Table V shows the reasons for rejecting these films. The overall acceptance rate was 90.1% of submitted films. In contrast, in the early phases of the study, the acceptance rate was as low as 71%. Protocol adherence and film quality improved after the reasons for rejection were reviewed with the clinical sites.

Baseline demographic characteristics of the 408 patients randomized are listed in Table VI.

TABLE VI Baseline Demographic Characteristics

	Group A	Group B
Mean age (years)	57	57
Range	37–75	33–72
Men/women (%)	76/24	79/21
Race (%)		
White	90	86
Other	10	14
Average total cholesterol (mg/dl)	229	232
Range*	172–294	175–294
Average low-density lipoprotein cholesterol (mg/dl)	162	165
Range*	119–220	113–208
Average high-density lipoprotein cholesterol (mg/dl)	41	41
Range*	23–98	25–70
Average triglycerides (mg/dl)	165	167
Range*	49–511	46–425

*Last observation before randomization.

DISCUSSION

PLAC I and other ongoing studies should help establish whether treatment of patients with moderately increased serum cholesterol levels slows progression of coronary artery disease and presumably prevents clinical events as much as in trials of those with severe hypercholesterolemia.[6,7] The positive or negative results should have important implications for the large number of patients with coronary artery disease but only moderate LDL cholesterol elevation.

Several features of the design and recruitment of patients in the trial deserve comment, and may bear on the design of future studies. Assessment of the progression of coronary artery disease was the primary aim. Thus, before randomization, each patient's angiogram was screened through the core angiography laboratory to ensure that the protocol was followed and that the angiogram could be sufficiently digitized to ensure adequate analysis at the end of 3-year follow-up. In the early phases of the study, >100 angiographers were participating, and variation in attention to contrast streaming and protocol adherence was considerable. After core laboratory personnel rejected several films, protocol adherence improved substantially. Table V documents the value of using this approach in conjunction with quantitative angiography to ensure adequacy of baseline films.

The most frequent reason for excluding patients from the study was low serum cholesterol (Table III). A large proportion of patients with documented coronary artery disease have cholesterol concentrations only modestly increased or within the range considered normal for the U.S. population. The data support conclusions from other studies[8,9] and have important implications not only for future trials but also for understanding the pathogenesis of coronary artery disease. Mechanisms other than hyperlipidemia, such as insulin resistance, may be of substantial pathophysiologic importance in patients with only moderate or no increase in serum LDL cholesterol. Although a lipid-lowering strategy such as monotherapy with pravastatin is likely to benefit patients with severe or moderately severe hypercholesterolemia, the effect of reducing lipids in those with only minimal or no increase in serum lipids despite coronary artery disease should be determined.

APPENDIX

Study organization: PARTICIPATING INSTITUTIONS AND PRINCIPAL INVESTIGATORS: *University of Michigan Hospital, Ann Arbor, MI:* Bertram Pitt, MD, Stephen G. Ellis, MD; *Henry Ford Hospital, Detroit, MI:* Howard S. Rosman, MD; *Sinai Hospital, Detroit, MI:* Melvyn Rubenfire, MD; *William Beaumont Hospital, Royal Oak, MI:* Gerald C. Timmis, MD; *Saint Joseph Hospital, Ann Arbor, MI:* Ronald Van den Belt, MD; *Deaconess Hospital, St. Louis, MO:* Harold L. Kennedy, MD; *Georgetown University Medical Center, Washington, D.C.:* Charles E. Rackley, MD; *Burns Clinical Research Foundation, Petoskey, MI:* Harry T. Colfer, MD; *Johns Hopkins University, Baltimore, MD:* Lewis C. Becker, MD; *Humana Heart Institute, Louisville, KY:* David A. Dageforde, MD; *Central Ohio Interventionists, Columbus, OH:* Richard J. Candela, MD; *New Mexico Heart Clinic, Albuquerque, NM:* George F. Leatherman, MD; *Washington Adventist Hospital, Tacoma Park, MD:* Robert DiBianco, MD; and *Core Angiography Laboratory University Hospital, University of British Columbia, Vancouver, British Columbia, Canada:* G. B. John Mancini, MD, Director.

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