The Effects of Lowering Upoprotelin(a) Levels with Nlacin on Cardiac Events and on the Progression of Coronary Artery Stenosis.

Ira D. Solomon

A. Purpose of Study

Lipoprotein(a) levels are correlated with the risk of atherosclerotic heart disease in certain populations. A combination of Niacin with Fluvastatin has previously been shown to significantly reduce levels of LP(a) by as much as 37% when compared to use of fluvastatin alone. In the Coronary drug project niacin was proven to decrease the incidence of secondary MI, and to reduce longterm mortality by 11%.

Their have however, been conflicting reports as to whether or not LP(a) is an independent risk factor for ASHD. In African American populations it has been found that their is no correlation between plasma LP(a) concentrations and the presence or absence of ASHD, whereas other studies report a higher incidence of ASHD in patients with higher levels of LP(a), especially in caucasian and asian populations. African Americans have a higher mean LP(a) level than caucasians but the rate of cardiac events are comparable. It is unclear therefore whether lowering the LP(a) level as an indepedant variable will always lower ones risk of cardiac events.

The Cholesterol Lowering Atherosclerosis Study (CLAS) using Niacin and Colestipol vs. placebo and the Monitored Atherosclerosis Regression Study (MARS) using Lovastatin vs. placebo have previously shown the beneficial effects of lipid lowering agents on the preogression of coronary ertery disease. Since lipid lowering agents have effects on multiple lippoproteins it is unclear whether or not LP(a) incured an increased risk in CAD or if LP(a) is simply a marker for CAD. If LP(a) is simply a marker and not involved in the pathogenesis of advancing CAD then lowering it will not decrease the progression of CAD.

The purpose of this study is to attempt to correlate the pharmacological reduction in LP(a) levels with a decrease in the risk of subsequent cardiac events (eg: MI), and assess the progression of coronary artery stenosis with lower LP(a) levels when compared to a control group.

B. Description of Study Design and Statistical Analysis

a. Methods for selecting the suboects to be entered n each experimental group

This study is a randomized controlled trial with patients selected who have a history of coronary artery disease in at least 2 segments with one lesion being at least a 50% stenosis. Patients were then assigned to either treatment with Niacin or Fluvastatin. This study wil be preceeded by a three month dosing schedule of Niacin and Fluvastatin of 30 patients that will obtain equivalent LDL level lowering. Progression of coronary artery disease will be assessed by cardiac catheterization using Quantitative Coronary Angiography(QCA) and a Global A Score.

There are no plans for crossing subjects over from one group to the other.

b. Randomization

Patients were randomly assigned with a sequential sample design and staggered enrollment into blocks defined by total plasma cholesterol (<240mg/dl) vs (>240mg/dl), sex smoking.

c. Measurement

We will measure the effect of lowering the LP(a) level by 30 to 40% in the treatment group on the progression of.CAD and on the incidence of cardiac events. The lowering of LP(a) in the treatment group will be accomplished over the first 6 weeks of the trial and their LP(a) levels will be maintained at this lower level for the duration of the trial. Total cholesterol and triglycerides were measured by

enzymatic assay kits. LP(a) levels were measured by use of a sandwich enzymelinked immunosorbent assay.

The primary endpoint of the study will be the average Δ from baseline in % diameter stenosis in all lesions that showed a 20% stenosis at baseline. This Δ will be assessed by Quatitative coronary angiography(QCA), which uses angiographic film pairs processed in tandem to match frames for degree of contrast filling. Lesions found by this method were assessed by a QCA analyst. Secondary endpoints will assess 1-avg. Δ in minimum luminal diameter by QCA, 2-Global Δ score (as asessed by experienced angiographers with 0=[no demonstrable Δ] and 3=[extreme Δ], 3-The proportion of pt's progression or regression of disease.

d. Statistical Analysis

Analysis of the primary endpoint, %Δ in stenosis 20% lesions, will be assessed by analysis of covariants.

Appropriateness of lipid lowering dosing regiment will be determined by a Student t-test comparison of the two groups.

The Student t-test, the Fisher exact test, and the chi-square test were used to compare treatment groups at baseline; to compare groups regarding global change score, the proportion of progressing and regressing patients, and the proportion of pt's with at least one new lesion and at least one new total occlusion; and to compare treatment groups reguarding the incidence of adverse experiences.

C. Description of Study Procedures

Each patient will be evaluated at 0 months, 1 mo, 2 mo's, 4 mo's, and every 4 mo's for the duration of the initial study period of 2yrs. At those times pt's will be evaluated for LP(a), lipid, and apolipoprotein levels. And also for the incidences of adverse experiences (ie-angina, acute MI). Cardiac cath. will take place within one month of entering the study, with subsequent cath. at 2 yrs. At the end of two years angiographic studies will be assessed for the primary and secondary endpoints and for the proportion of pt's with at least one new lesion or occlusion. Standard clinical care only requires repeat cath. if the~js a symptomatic progression of a patient's CAD.

The entire study will last 4 to 6 years with each subject participating for 2yrs.

D. Study Drugs

Group	Drug	Dosing	Side Effects
Group A	Niacin	• 1 00mg titrate during a period of two weeks from 1 00mg to • 500mg 3 times daily after meals, to a maximum of 1 g 3 times daily from week 8 to 16	• may include : ○ pruritis ○ flushing ○ headaches,paresthesias ○ nausea. • Large doses may : ○ activate peptic ulcer ○ impair glucose intolerance ○ produce liver damage ○ produce hyperuricemia.
Group B	Fluvastatin (Lescol)	• X mg once a day at bedtime (> 2 hours after the evening meal) Appropriate dose to be ascertained during pre-study scheduling trial	• potential myopathy • contraindicated in pt's with cholestasis or a history of liver disease

E. Medicall Devices

Cardiac catheterization at 0 and 2 years

F. Study Questionnaires

A questionnaire will be developed to determine a patient's eligibility to enter this trial as determined by the inclusion/ exclusion criteria. At 4 mo's intervals pt's will also be given questonaires concerning adverse cardiac events in the preceeding 4 mo's.

G. Description of Study Subjects and Method of Recruitment

Population- Patients were enrolled in the study if they were <70 yrs of age and had a history of coronary artery disease in at least 2 segments, with at least 1 showing diameter stenosis of 50% or more unaltered by PTCA. Pt's also had a history of borderline to high total cholesterol (190 - 295mg/dl). Patients were identified eitherthrough th6ir admission to CPMC or by referral of their primary physician. The former were approached in hospital and given a letter to take to their primary MD stating their eligibility for the study.

a. Inclusion/Exclusion Criteria

- Hypertension (with diastolic BP>1 15)
- Diabetes Mellitus
- Use of lipid lowering drugs within 2 months of randomization
- CABG candidates were excluded

b. Minority Groups

African American subjects will be excluded from this trial. Some previous reports have shown no increased risk of CAD in African American population with higher LP(a) levels, whereas in Caucasian and Oriental populations, increased LP(a) levels confer an increased risk of CAD. At this point it would be unethical to subject African Americans to treatment with niacin which has no proven benefit and potential side effects in that population.

c. Number of Subjects To Be Enrolled

As in the MARS trial the primary endpoint of this study is the average change from baseline in percent diameter stenosis in all lesions that show a 20% stenosis at baseline. Power calculations based on this endpoint (SD est. 6 -8%) indicate an effective sample size of ***250*** patients had at least an ***80**% power to detect a treatment difference of 2 - 3% in diameter stenosis at the 0.05 significance level (2 sided).

d. Vulnerable Polpulations

Such as minors, the elderly, pregnant women, prisoners, patients who are institutionalized, or unable to give consent will not be enrolled in this study.

H. Confidentiality of Study Data

Each study subject will be identified using a unique code number and all study data will be referred to by that code. Names, Hospital Unit numbers, social security numbers, addresses, and phone numbers will not be used as personal identifiers. All identifying data will only be accessible to the investigators.

I. Location of Study

Multi-center community and university based cardiac catheterization laboratories.

J. Risks and Benefits

Since cardiac catheterization is an invasive technique, the potential complications include death, myocardial infarction, stroke, perforation of the heart or the great vessels, and local vascular problems. Those who are at increased risk during cath. are age <1, or > 70, CHF class IV, left main CAD, valvular heart disease, LV dysfunction with EF < 30%, and severe noncardiac disease (ex. RI, IDDM,CVA,PVD).

Side effect profiles of the medications used in this trial have been presented above.

K. Alternative Therapies

This trial is assessing at the efficacy of using Niacin to lower LP(a) levels and cardiac event , CAD outcomes. The only other known medical therapy with similar effects on LP(a) levels is Neomycin. This drug however is not commonly used to treat hyperlipidemia because of a high incidence of diarrhea and the potential for ototoxicity.

L. Compensation and Cost to Subjects

This trial will involve no compensation or cost to the subject.

M. Minors and Research Subjects

No minors will be involved in this study.

N. Radiation or radioactive substances

During cardiac angiography radiopaque contrast agent will be injected into either a specific cardiac chamber or vessel using either hand injection or power injection through an automated syringe. A history of allergic reaction to radiographic contrast agents, which may range from urticaria to frank anaphylactic reaction, is an important relative contra indication to cardiac catheterization, which requires appropriate pretreatment. This may involve the use of glucocoticoids, antihistamines, and H-2 blockers.