ARIC Manuscript Proposal # 889

PC Reviewed: 06/18/02	**Status: __A__**	**Priority: __K__**
SC Reviewed: 06/18/02	**Status: __A__**	**Priority: __K__**

1.a. Full Title: Plasma Lipoprotein-Associated Phospholipase A_2 (Lp-PLA_2) Concentration and Incident CHD in Middle-Aged Men and Women: The ARIC Study

b. Abbreviated Title (Length 26 characters): Lp-PLA_2 and incident CHD

2. Writing Group (list individual with lead responsibility first):

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3. Timeline: Measurement of plasma lipoprotein-associated phospholipase A_2 (Lp-PLA_2) will be performed in March of 2002 on plasma from visit 2 for coronary heart disease (CHD) cases and cohort random sample (CRS) controls. Statistical analyses will be completed in June of 2002 and manuscript will be completed by September of 2002.

4. Rationale:

The hypothesis that atherosclerosis is an inflammatory disease is supported by both the discovery of inflammatory cells in the cap of atherosclerotic plaques and recent reports that elevated levels of plasma markers of inflammation are associated with incidence of CHD (Ross, 1999). The oxidative modification of low-density lipoproteins (LDL) within the arterial wall is a key early event in the development of atherosclerosis (Witztum and Steinberg, 1991). Therefore, numerous studies have focused on enzymes that are involved in the oxidation of LDL and, as a result, alter the pro-inflammatory activities of oxidized LDL (oxLDL). The LDL oxidation process involves the oxidation of the polyunsaturated fatty acid component of phospholipids and ultimately leads to the conversion of phosphatidylcholine (PtdCho) to lyso-PtdCho (Parthasarathy et al., 1985). The increased lyso-PtdCho content of oxLDL is a chemoattractant for human monocytes and induces endothelial dysfunction (Quinn et al., 1988; Kume et al., 1992).

Lp-PLA_2, also known as platelet-activating factor (PAF) acetylhydrolase, is a serine-dependent lipase that has been shown to hydrolyze oxidatively modified PtdCho to release oxidized fatty acids and lyso-PtdCho (Stremler et al., 1991). Lp-PLA_2 co-purifies with LDL and is responsible for >95% of the phospholipase activity associated with LDL (Tew et al., 1996). Its expression is regulated by mediators of inflammation and inhibition of Lp-PLA_2 activity results in a significant decrease in both lyso-PtdCho content and monocyte chemoattractant ability of oxLDL (Cao et al., 1998; Tew et al., 1996).

The role of Lp-PLA_2 in the development of atherosclerosis is currently not clearly understood, since the enzyme could promote atherogenesis if the oxidative products released from oxLDL have deleterious effects on the arterial wall, or Lp-PLA_2 could be anti-atherogenic if, in hydrolyzing PAF, it reduces inflammation.

The West of Scotland Coronary Prevention Study (WOSCOPS) has investigated the predictive value of plasma levels of Lp-PLA_2 for CHD (Packard et al., 2000). WOSCOPS enrolled 6,595 men with elevated LDL-C (174–232 mg/dl) who were randomly assigned to receive pravastatin or placebo. In a case–cohort study, baseline levels of Lp-PLA_2 were measured in 580 CHD cases (defined by nonfatal MI, death from CHD, or a revascularization procedure) and 1,160 contols matched for age and smoking status. Plasma levels of Lp-PLA_2 were significantly associated with development of CHD events by univariate and multivariate analyses with almost a doubling of the relative risk for CHD events for the highest quintile of Lp-PLA_2 compared to the lowest quintile. Although this report found Lp-PLA_2 to be an independent predictor of CHD, the interpretation of these results is limited because of the design of the study. WOSCOPS is a prospective study that enrolled middle-aged white men with pre-existing hypercholesterolemia who were living in the West of Scotland, a region with a diet notoriously high in cholesterol and fat. The results may not be applicable to the general population of the United States.

More recently,

We postulate that elevated plasma levels of Lp-PLA_2 are associated with incidence of CHD. To test this hypothesis, we propose to determine the plasma levels of Lp-PLA_2 in CHD cases and control subjects enrolled in the Atherosclerosis Risk in Communities (ARIC) study, using a newly developed sandwich ELISA assay (diaDexus, Inc).

References:

Cao Y, Stafforini DM, Zimmerman GA, McIntyre TM, Prescott SM. Expression of plasma platelet-activating factor acetylhydrolase is transcriptionally regulated by mediators of inflammation. J Biol Chem 1998;273:4012-4020.

Kume N, Cybulsky MI, Gimbrone MA Jr. Lysophosphatidylcholine, a component of atherogenic lipoproteins, induces mononuclear leukocyte adhesion molecules in cultured human and rabbit arterial endothelial cells. J Clin Invest 1992;90:1138-1144.

Packard CJ, O'Reilly DS, Caslake MJ, McMahon AD, Ford I, Cooney J, Macphee CH, Suckling KE, Krishna M, Wilkinson FE, Rumley A, Lowe GD, for the West of Scotland Coronary

Prevention Study Group. Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. N Engl J Med 2000;343:1148-1155.

Parthasarathy S, Steinbrecher UP, Barnett J, Witztum JL, Steinberg D. Essential role of phospholipase A2 activity in endothelial cell-induced modification of low density lipoprotein. Proc Natl Acad Sci U S A 1985;82:3000-3004.

Quinn MT, Parthasarathy S, Steinberg D. Lysophosphatidylcholine: a chemotactic factor for human monocytes and its potential role in atherogenesis. Proc Natl Acad Sci U S A 1988;85:2805-2809.

Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115-126.

Stremler KE, Stafforini DM, Prescott SM, McIntyre TM. Human plasma platelet-activating factor acetylhydrolase. Oxidatively fragmented phospholipids as substrates. J Biol Chem 1991;266:11095-11103.

Tew DG, Southan C, Rice SQ, Lawrence MP, Li H, Boyd HF, Moores K, Gloger IS, Macphee CH. Purification, properties, sequencing, and cloning of a lipoprotein-associated, serine-dependent phospholipase involved in the oxidative modification of low-density lipoproteins. Arterioscler Thromb Vasc Biol 1996;16:591-599.

Witztum JL, Steinberg D. Role of oxidized low density lipoprotein in atherogenesis. J Clin Invest 1991;88:1785-1792.

5. Main Hypothesis/Study

Elevated levels of plasma Lp-PLA_2 are associated with increased risk for CHD events in both men and women.

Secondary Hypotheses*:* 1) Plasma levels of Lp-PLA_2 are associated with increased risk for developing CHD after adjusting for traditional risk factors (HDL cholesterol, total cholesterol, triglycerides, diabetes, cigarette-years of smoking, BMI, systolic blood pressure, physical activity, HRT) and hs-CRP.

2) Following adjustment for traditional risk factors, plasma Lp-PLA2 is a stronger independent predictor for CHD events than hs-CRP.

6. Data (variables, time window, source, inclusions/exclusions):

Lp-PLA2 and hs-CRP will be measured in Visit 2 plasma samples of CHD cases and cohort random sample (CRS).We are currently defining the CRS from persons attending the second ARIC examination who had not experienced CHD or stroke by that exam. That CRS is stratified by age, sex, and race (blacks and whites). In addition, total cholesterol and triglycerides will be measured in a subset of Visit 2 plasma samples (5% of all samples tested, randomly selected) that were previously tested for quality control purposes. Data will include incident CHD case status and date of CHD diagnosis. Covariates will include visit 2 age, gender, race, center, BMI, cigarette-years of smoking, HDL cholesterol, total cholesterol, triglycerides, diabetes, systolic blood pressure, physical activity, HRT, inflammatory markers (WBC, fibrinogen, TNF-α, MMP-1, TIMP-1).

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

___X___ Yes _____ No