1.a. **Full Title:** Plasma Concentrations of P-selectin and L-selectin and Risk for Coronary Heart Disease (CHD).

b. **Abbreviated Title (Length 26 characters):** P-selectin and L-selectin and incident CHD

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

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3. **Timeline:** All sample analyses have been completed by the Lipid Laboratory. Statistical analysis will start February, 2002 and manuscript will be completed by August 2002.

4. **Rationale:**

   Atherosclerosis is a chronic inflammatory process that involves complex interactions of vascular endothelium with platelets and leukocytes (Ross, 1999; Price et al., 1999). Cellular adhesion molecules in response to inflammatory stimuli predominantly mediate this process. P-selectin and L-selectin belong to the selectin family of adhesion molecules that are produced by a variety of cell types including platelets, leukocytes and vascular endothelial cells, and mediate the transient rolling of leukocytes along the vascular endothelium, which leads to the recruitment of circulating leukocytes to vascular sites of inflammation (Tedder et al., 1995). It is believed that subsequent migration of leukocytes into the subendothelial cell layer and accumulation of lipids within these cells leads to formation of lipid-laden foam cells and fatty streaks, the initial step in the development of atherosclerosis.

   Support for a role of P-selectin in the etiology of atherosclerosis stems from studies that show increased expression of P-selectin in the endothelium overlying atherosclerotic
plaques but not in endothelium overlying inactive fibrous plaques or normal arterial endothelium (Johnson-Tidey et al., 1994). Furthermore, P-selectin deficient mice exhibit delayed fatty streak formation (Johnson et al., 1997) and apoE or LDL-receptor deficient mice that are also deficient for P-selectin show significant reductions in atherosclerotic lesion sizes (Dong et al., 2000; Johnson et al., 1997).

Soluble forms of P-selectin (sP-selectin) exist as a result of proteolytic cleavage or alternative splicing and elevated levels of sP-selectin have been found in various cardiovascular disorders, including unstable angina, hypercholesterolemia, and peripheral vascular disease. A report from the Women’s Health Study indicates that women with elevated sP-selectin levels may be at increased risk for future cardiovascular events (Ridker et al., 2001). However, results from the AtheroGene Study, which studied both men and women with or without coronary artery disease (CAD), suggest a complex age-dependent association between sP-selectin levels and coronary artery disease (Barbaux et al., 2001).

The role of L-selectin in the development of atherosclerosis is poorly understood. L-selectin is expressed on leukocytes and mediates the tethering and rolling of leukocytes along the activated vascular endothelium (Puri et al., 1997). Few data is available on changes in sL-selectin plasma levels in different cardiovascular disorders. Low levels of sL-selectin have been observed in acute myocardial infarction (AMI) and angina pectoris, which may be related to a depressed expression or decreased shedding of L-selectin from leukocytes (Haught et al., 1996). A recent study showed significant lower levels of sL-selectin in type 2 diabetes patients with symptomatic CAD and silent myocardial ischemia (SMI) when compared to healthy control subjects (Albertini et al., 1999). These results indicate that sL-selectin levels may be a marker for silent CAD in type 2 diabetic patients. Decreased levels of sL-selectin were also found in 42 patients with peripheral artery disease (PAD) when compared to 42 age and sex matched controls, although this decrease did not reach significance (Blann et al., 1996).

In summary, to date there is very limited data available from prospective epidemiologic studies on the relationship of plasma P- and L-selectin levels and incidence of CHD. Therefore, we propose to investigate the association of plasma levels of P- and L-selectin with incident CHD.

References:


5. **Main Hypothesis/Study Questions:**

Increased plasma concentrations of sP-selectin and decreased plasma concentrations of sL-selectin are associated with increased risk for CHD events and peripheral arterial disease (PAD), as well as increased carotid artery thickness.

Secondary hypotheses are:

A) increased plasma levels of sP-selectin and decreased plasma levels of sL-selectin are associated with markers of inflammation (WBC, VCAM-1, ICAM-1, CRP, fibrinogen, E-selectin,).

B) increased ratio of sP-selectin: sL-selectin is associated with increased risk for CHD events and peripheral arterial disease (PAD), as well as increased carotid artery thickness.

C) decreased plasma levels of sL-selectin are associated with increased risk for type 2 diabetes mellitus.

6. **Data (variables, time window, source, inclusions/exclusions):**
sP-selectin and sL-selectin measurements were made on Visit 1 plasma samples of CHD cases, cohort stratified random sample (CRS), PAD, African American, MRI, and 3-group. Data will include incident CHD case status and date of CHD diagnosis. Covariates will include visit 1 age, gender, race, center, BMI, years of cigarette smoking, incident diabetes, triglycerides, LDL cholesterol, HDL cholesterol, inflammatory markers (WBC, ICAM-1, VCAM-1, fibrinogen, CRP, E-selectin).

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](http://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html)

  ____X__  Yes  ______ No