1.a. Full Title: Circulating levels of CD40 ligand (CD154) and ICAM-1 and Incident Coronary Heart Disease in Middle-Aged Men and Women: The ARIC Study

b. Abbreviated Title (Length 26 characters): CD40 ligand and ICAM-1 and incident CHD

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

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   Other writing group members are invited to join

3. Timeline: Measurements of plasma CD40 ligand and ICAM-1 concentrations were completed in July of 2002 on plasma from visit 2 for 609 coronary heart disease (CHD) cases and 741 cohort random sample (CRS) controls. Statistical analyses will start in the summer of 2003 and manuscript completion is projected for the Fall of 2003.

4. Rationale:

   Recent studies indicate that inflammatory processes play a key role in the etiology of cardiovascular disease. Central to the inflammation hypothesis is that vascular endothelium injury induced by oxidant stress, diabetes, infectious microorganisms, and other factors, leads to endothelial dysfunction. This endothelial dysfunction elicits an inflammatory response that results in the recruitment of leukocytes and migration of smooth muscle cells to the site of injury through the expression of cellular adhesion molecules, chemokines, cytokines, and growth factors.

   Increasing evidence supports a central role for the immune-signaling dyad CD40 receptor / CD40 ligand in the etiology of atherosclerosis, thrombosis, and inflammation. CD40 ligand is a 39-kDa transmembrane protein and member of the tumor necrosis factor (TNF) family. The interactions between CD40 receptor and CD40 ligand were originally thought to involve B and T
cells, but more recently it has been shown that functional CD40 ligand and CD40 receptor molecules are also expressed on human vascular endothelial cells, smooth muscle cells, and macrophages.\(^3\) Disruption of the CD40 receptor / CD40 ligand dyad in LDL-receptor or Apo E-deficient mice prevents initiation of atherosclerosis and atherosclerotic lesion progression to more advanced lesions.\(^4\) Circulating levels of soluble CD40 ligand have been found to be associated with the extent of intraplaque lipid accumulation in patients with carotid atherosclerosis as determined by high-resolution magnetic resonance imaging (MRI).\(^5\) Furthermore, in a prospective, nested case-control evaluation of apparently healthy middle-aged women in the Women’s Health Study (WHS), mean concentrations of sCD40L were positively correlated with future cardiovascular events.\(^6\)

Recently, Peng and coworkers found elevated levels of soluble CD40 ligand in patients with acute coronary syndrome when compared to control subjects and patients with stable coronary heart disease (CHD), which were positively correlated with circulating levels of soluble intercellular adhesion molecule-1 (ICAM-1), triglycerides, and apoB, and negatively correlated with HDL-cholesterol.\(^7\) Previously, we have found that elevated circulating levels of intercellular adhesion molecule-1 (ICAM-1) were associated with incident CHD in a smaller sample of 204 CHD patients and 316 control subjects of the Atherosclerosis Risk In Communities (ARIC) Study.\(^8\) Therefore, we propose to evaluate the association of plasma levels of CD40 ligand and ICAM-1 with incident CHD in African-American and Caucasian men and women enrolled in the Atherosclerosis Risk in Communities (ARIC) study. The proposed study will also evaluate the predictive value of CD40 ligand and ICAM-1 for incident CHD in comparison to traditional and inflammatory risk factors for cardiovascular disease.

References:


5. Main Hypothesis/Study Questions:

Elevated levels of plasma CD40 ligand and ICAM-1 are associated with increased risk for CHD events in both men and women in simple models adjusted for age, gender, and race.

Secondary Hypotheses:

Plasma levels of CD40 ligand and ICAM-1 are positively correlated and 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).

We will compare the strength of association of CD40 ligand and ICAM-1 with incident CHD in comparison with other inflammatory markers including, hs-CRP, fibrinogen, WBC, IL-6, and TNF-α. We will also examine whether individuals with high levels of both ICAM-1 and CD40 ligand have a greater risk than individuals with elevated levels of only 1 of the 2 analytes.

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

CD40 ligand, and ICAM-1 have been measured in Visit 2 plasma samples of CHD cases and cohort random sample (CRS). The CRS includes persons attending the second ARIC examination who had not experienced CHD or stroke by that exam. The CRS is stratified by age, sex, and race (African-Americans and whites). 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, and inflammatory markers (hs-CRP, WBC, fibrinogen, ICAM-1, IL-6, TNF-α, MMP-1, TIMP-1).

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  ____ 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  ____ 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

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?


11. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.