ARIC Manuscript Proposal # 1094

PC Reviewed: _08/30/05	**Status: _____**	**Priority: ____**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Cyclooxygenase 2 Gene Polymorphism and Coronary Heart Disease in the Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters): Cox-2 Polymorphism and Heart

2. Writing Group:

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3. Timeline:

Statistical Analysis: Jul 05-Sept 05
Manuscript Preparation: Sept 05-Oct 05
Manuscript Revision: Nov 05-Dec 05
Mauscript Submission: Dec 05

4. Rationale:

Coronary heart disease (CHD) is a complex disorder characterized by variable gene expression and by intermediate phenotypes, such as coronary atherosclerosis. A

hallmark feature of atherosclerosis is inflammation mediated by prostaglandins (PGs) catalyzed by the enzyme cyclooxygenase (COX). COX converts arachidonic acid to the unstable intermediate prostaglandin PGH2. PGH2 is a precursor of several biologically active prostanoids, including PGI_2 and thromboxane (TX) A_2. They both influence the development of atherosclerosis by modulating the inflammatory response, the expression of metalloproteinases, and the growth of cells implicated in the process, such as vascular smooth muscle cells.

There are at least 2 COX genes coding the different enzymes: COX-1 and COX-2. COX-1, expressed constitutively in most tissues, is thought to release PGs involved in housekeeping functions, such as the maintenance of gastrointestinal tract and vascular homeostasis. COX-2, undetectable in most tissues, can be upregulated by bacterial lipopolysaccarides, cytokines, growth factors, and tumor promoters, suggesting its relevance to both acute and chronic inflammation. Its expression is enhanced in endothelial cells of patients with CHD leading to enhanced production of matrix metalloproteinases in atherosclerotic plaques.

The role of COX-2 in atherogenesis is controversial. COX-2 inhibitors have been shown variously to retard, accelerate, fail to accelerate, or leave unaltered atherogenesis in LDLR and ApoE KO mice. Clinically, inhibition of the COX is known to afford relief of symptoms in the inflammatory arthritides, but recent placebo-controlled trial of rofecoxib revealed a 2-fold increase of myocardial infarction and stroke that led to withdrawal of the drug from the market.

A limited number of polymorphisms in the COX-2 promoter region have been identified. We wondered whether COX-2 polymorphism could contribute to altered prostaglandin biosynthesis in distinct CHD such as myocardial infarction. A recent large scale genomic study found protective effect of a G765C polymorphism against myocardial infarction and stroke. However, this study did not use a population-based or prospective sample, nor was it able to adequately account for the ever-present issue of multiple comparisons. The results of such hypothesis generating studies require validation in population-based prospective studies of incident CHD, such as that afforded by the ARIC study.

5. Main Hypothesis/Study Questions:

1. To estimate the frequency distribution of COX-2 gene variation in a population-based sample of whites and blacks.
2. In a race specific manner, to test the ability of COX-2 gene variation to predict incident CHD. These analyses will be carried out taking into account gender and age, and after controlling for other established risk factors.
3. In a race specific manner, to test the ability of COX-2 gene variation to predict incident stroke. These analyses will be carried out taking into account gender and age, and after controlling for other established risk factors.

4. If the results of either aim 2 or aim 3 are significant, we will examine whether the relationship between COX-2 gene variation and incident disease are modified by hsCRP levels. Note that the authors are aware that hsCRP was measured on visit 2 plasma, so that visit 2 will become the new "baseline" time point.

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

ARIC's stroke and CHD incident case status will be the primary dependent variables. The usual prevalent disease and missing data exclusion criteria will be used. Independent variables include, but are not limited to, COX-2 G765C genotype status and traditional risk factors such as field center, age, gender, race, smoking status, plasma lipid levels, body mass index, and hypertension and diabetes status. Finally, hsCRP level will be used for effect modification analyses.

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

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

10. What are the most related manuscript proposals in ARIC?
N/A

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ No

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* _____)
___ B. primiarly based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____)

12. 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.