ARIC Manuscript Proposal #2232

PC Reviewed: 9/10/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Circulating levels of liver enzymes and incidence of atrial fibrillation: the ARIC study

b. Abbreviated Title (Length 26 characters): Liver enzymes and AF

2. Writing Group:

Writing group members: Alvaro Alonso, Jeffrey Misialek, Mohamed Amin, Ron Hoogeveen, Lin Chen, Sunil Agarwal, Laura Loehr, Elsayed Soliman, Elizabeth Selvin

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. AA **[please confirm with your initials electronically or in writing]**

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3. Timeline: We aim to submit this manuscript to the ARIC publications committee in <4 months from this date.

4. Rationale:

Atrial fibrillation (AF) is the most commonly diagnosed cardiac arrhythmias in clinical practice. It affects >2 million people in the United States, and this figure is projected to double by 2050.[1] Individuals with AF are at a substantially increased risk of stroke and overall mortality.[2] Therefore, considerable interest exists in identifying risk factors and biomarkers of AF. To date, numerous studies have shown that multiple variables contribute to an elevated risk for AF, including major cardiovascular risk factors and biomarkers involved in diverse pathways.[3-6]

Liver enzymes could be a potentially novel biomarker of AF risk. Circulating liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are indicative of hepatocellular homeostasis and injury, and gamma glutamyl transpeptidase (GGT) reflects both liver injury and oxidative stress. Prior epidemiologic evidence suggests that blood liver enzymes, even in individuals without overt hepatic disease, might be associated with an increased risk of cardiovascular disease (CVD),[7] potentially due to their role as markers of nonalcoholic fatty liver disease (NAFLD).[8]

A recently published analysis from the Framingham Heart Study showed that higher levels of both ALT and AST were associated with an increased risk of AF, independently of alcohol consumption, among individuals free of clinical heart failure.[9] This association, however, needs to be replicated in large, independent prospective studies conducted in diverse populations. Also, no previous studies have assessed the association of GGT with AF incidence.

5. Main Hypothesis/Study Questions:

Our objective is to assess the association of plasma liver enzymes (ALT, AST, GGT) with AF incidence in the Atherosclerosis Risk in Communities (ARIC) study. We hypothesize that higher levels of circulating liver enzymes will be associated with a higher risk of AF.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design

We will conduct a follow-up study of ARIC participants examined in visit 4, free of AF at that time, with available data on liver enzymes.

Main outcome variable

Incident AF between visit 4 and end of 2010, identified from ICD9CM codes 427.31 and 427.32 in hospital discharges and ICD9 427.3 or ICD10 I48 from death certificates.

Main exposure

ALT, AST and GGT measured in visit 4. Liver enzymes will be analyzed as continuous variables, by quintiles, and by clinical cut-points as recommended by the lab.

Other covariates

We will consider the following variables as potential confounders: age, sex, race, study site, education, smoking, alcohol intake, body mass index, height, systolic blood pressure, diabetes, use of antihypertensive medication, prevalent CHD or heart failure, C-reactive protein, and NT-proBNP.

Statistical analysis

We will use Cox proportional hazards model to estimate hazard ratios and 95% confidence intervals for the association between liver enzymes and risk of AF. Initial

models will adjust for age, sex, and race. Other potential confounding variables will be added in subsequent models.

In sensitivity analyses, we will exclude individuals with elevated alcohol consumption (>2 drinks/day in men, >1 drink/day in women), and those with prevalent heart failure.

We will explore interactions by age, sex, race, and body mass index.

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 ICTDER03 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 ICTDER03 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 ICTDER03 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://www.cscc.unc.edu/ARIC/search.php

___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)?

ARIC Manuscript Proposal # 1833: Liver enzymes and incident CVD
ARIC Manuscript Proposal # 1789: Elevated Liver Enzymes and Risk of Diabetes
ARIC Manuscript Proposal # 977: Liver Enzyme Activity and Risk of Diabetes

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

11.b. If yes, is the proposal

_X_ A. primarily the result of an ancillary study (list number* 2008.12)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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7. Fraser A, Harris R, Sattar N, Ebrahim S, Smith GD, Lawlor DA. Gamma-glutamyltransferase is associated with incident vascular events independently of alcohol intake: analysis of the British Women's Heart and Health Study and meta-analysis. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2007;27:2729-2735.
8. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med.* 2010;363:1341-1350.
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