

**ARIC Manuscript Proposal #2231**

**PC Reviewed: 9/10/13**  
**SC Reviewed: \_\_\_\_\_**

**Status: A**  
**Status: \_\_\_\_\_**

**Priority: 2**  
**Priority: \_\_\_\_\_**

**1.a. Full Title:** Alcohol consumption and Cardiac Structure and Function

**b. Abbreviated Title (Length 26 characters):** Alcohol and left ventricular function.

**2. Writing Group:**

Writing group members: Alexandra Gonçalves, Pardeep S. Jhund, Brian Claggett, Amil M Shah, Wayne Rosamond, Flavio Fuchs, Scott D. Solomon, others welcome

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

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**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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**3. Timeline:** Analysis will begin following proposal approval. Anticipating completion of echocardiography of ARIC Visit 5 cohort in 2013, a manuscript will be completed within 6 months of the date.

#### **4. Rationale:**

Alcohol consumption has been known to lead to alcoholic cardiomyopathy. Conversely, light-moderate drinking seems to have benefits in coronary heart disease<sup>1</sup> and may protect against the development of heart failure (HF).<sup>2, 3</sup>

There are limited data on the amount and duration of consumption required to produce symptomatic alcoholic cardiomyopathy and the pathophysiologic mechanisms underlying alcoholic left ventricle (LV) function impairment are poorly understood. The most relevant mechanisms by which alcohol consumption may cause myocardial damage are the ethanol induced apoptosis leading to myocytes loss,<sup>4</sup> the acetaldehyde myocardial depression through mitochondrial dysfunction, oxidative damage, impaired Ca<sup>2+</sup> homeostasis<sup>5, 6</sup> and the activation of the renin angiotensin system.<sup>7</sup>

Established alcoholic cardiomyopathy is characterized by pronounced LV dilatation, increased LV mass, thin LV walls and significant systolic impairment at the symptomatic phase.<sup>8, 9</sup> However, the earlier stage of LV dysfunction by alcohol consumption has been poorly addressed and it is unknown if moderate-heavy drinkers present LV dysfunction regardless of preserved LV ejection fraction. Recently, a clinical magnetic resonance imaging study reported reversible myocardial injury with myocardial hyper enhancement after binge drinking, but without decrease in LV systolic function.<sup>10</sup> Two dimensional (2D) speckle tracking echocardiography is a relatively new technique for myocardial deformation analysis, which can detect LV systolic function abnormalities in heart disorder patients without an abnormal LV ejection fraction.

Conversely, it is likely that currently genetic factors contribute to the susceptibility to alcoholic cardiomyopathy.<sup>11</sup> Previous reports suggest that the alcohol-metabolizing genes, the alcohol dehydrogenase (ADH) and cytochrome P4502E1 (CYP2E1) pathways may influence the association between alcohol consumption and cardiovascular disease.<sup>12, 13</sup> The class I and II ADH genes (ADH1B, ADH1C, ADH4), the aldehyde dehydrogenase genes (ALDH1, ALDH2), and the CYP2E1 gene are the most studied up to now. Understanding genetic modifiers of the relation between alcohol consumption and early stages of HF would contribute to the recognition of the groups more likely to develop alcoholic cardiomyopathy.

There is an ARIC ancillary proposal (# 1635) entitled "Variation in alcohol-metabolizing genes modifies the relationship between steady alcohol consumption and incidence of CVD" and in consequence of the ARIC ancillary study (2006.09), the entire ARIC cohort has been genotyped for 40 SNPs in alcohol-metabolizing genes.

In this study we focus in heart failure and LV function and we propose to investigate if patients with moderate-to heavy alcohol consumption present LV dysfunction as an earlier stage of alcoholic cardiomyopathy, considering the modifying effect of alcohol-metabolizing genes.

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

1. Moderate-heavy alcohol consumption impairs LV function assessed by 2D speckle-tracking.
2. Mild alcohol consumption has no significant effect in LV function.
3. LV function impairment among alcohol consumers is affected by genetic variation in alcohol-metabolizing genes.

## **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).**

This study will analyze ARIC cohort participants that both presented to visit 1 and to visit 5, who have acceptable echocardiography image quality for analysis.

Participants will be excluded if they have previous history of heart failure at baseline, who were neither White nor African American and with inadequate measures of alcohol intake or with missing data for genotype data, or other covariates utilized in the analysis.

### **Variables to be evaluated**

#### Dependent variables:

Left ventricular systolic function evaluated by ejection fraction, tissue Doppler and speckle-tracking based strain (longitudinal, circumferential and radial). In secondary analyses, we will also consider LV mass, LV diastolic function parameters, the presence of valvular heart disease and the relation with cardiac biomarkers of heart failure (NT-proBNP and high sensitivity troponin T).

The independent variable of exposure will be alcohol consumption (continuous - grams/week as well as categorized- never / low-moderate / heavy; never/former/current drinker) classified during the period from visit 1 to visit 5. Additionally we will consider the exposure of the type of beverage (beer, wine and liquor)

Potential covariates: demographic characteristics (age, race, sex, body mass index, socioeconomic status), cardiovascular risk factors (diabetes, arterial hypertension, smoking, dislipidemia, family history of heart failure), incidence of acute myocardial infarction, use of antihypertensive medications or statins, plasma lipid levels (i.e. HDL and LDL cholesterol, apolipoprotein AI and B, triglycerides), clotting factors and alcohol-metabolizing genes.

### **Analytical approach:**

Continuous normally distributed data will be displayed as mean and standard deviation and continuous non-normally distributed data will be displayed as median and interquartile range. Categorical data will be shown as a total sample and proportion. Associations of alcohol consumption and primary echocardiographic outcomes (LV ejection fraction, LV tissue Doppler and LV strain) will be evaluated using linear regression and multivariable logistic regression

analyses adjusting for the significant covariates: demographic characteristics, cardiovascular risk factors, history of acute myocardial infarction, use of antihypertensive medications or statins, plasma lipid levels, clotting factors and alcohol-metabolizing genes.

In secondary analyses, we will assess the associations of alcohol consumption and LV mass, LV diastolic function parameters, the presence of valvular heart disease and the relation with cardiac biomarkers of heart failure (NT-proBNP and high sensitivity troponin T). Linear regression and multivariable logistic regression analyses adjusting for the significant covariates will be applied. P values < 0.05 will be considered significant.

**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 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  No

**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.csc.unc.edu/ARIC/search.php>**

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)?**

Variation in alcohol-metabolizing genes modifies the relationship between steady alcohol consumption and incidence of CVD. # 1635

Genome-Wide Association Study of Alcohol Consumption in the CHARGE Consortium. # 1651

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?**

Yes     No

**11.b. If yes, is the proposal**

A. primarily the result of an ancillary study (list number\* \_\_\_\_\_)

B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)\* (2006.09) \_\_\_\_\_)

\*ancillary studies are listed by number at <http://www.csc.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.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

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