ARIC Manuscript Proposal #2247

PC Reviewed: 10/8/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Alcohol consumption and risk of heart failure

b. Abbreviated Title (Length 26 characters): Alcohol and heart failure.

2. Writing Group:

Writing group members: Alexandra Gonçalves, Pardeep S. Jhund, Brian Claggett, Wayne Rosamond, Anita Deswal, David Aguilar, Amil M Shah, Susan Cheng, 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:

Heart failure (HF) is major public health issue. There is an estimate of 23 million people with HF worldwide[1] and according to the American Heart Association [2] there were 5.1 million people with HF in the United States in 2006.[3]
Amongst modifiable lifestyle factors, alcohol consumption has been known to lead to alcoholic cardiomyopathy. Conversely, light-moderate drinking seems to have benefits in coronary heart disease [4] and may protect against the development of HF.[5, 6] However, in patients with LV dysfunction after acute myocardial infarction, light-to-moderate alcohol intake did not alter the risk for the development of HF.[2] Moreover, there are limited data on the amount and duration of consumption required to produce symptomatic alcoholic cardiomyopathy and the association between beverage types, patterns of drinking and HF remains inconsistent.[7] Additionally, light-moderate drinking benefits are not clear in woman[8] or in African-Americans. The results form ARIC cohort followed up between 1987 and 1998 showed a positive association between ethanol consumption and incident coronary heart disease for Black men and an inverse association for White men. [9]

The factors responsible for the apparent cardiovascular benefits of light to moderate alcohol intake are uncertain, but anti-oxidant, anti-inflammatory, antithrombotic and anti-dyslipidemic effects might be involved. Previous studies described that alcohol consumption results in increase of serum HDL-cholesterol, apolipoprotein A-I, plasminogen and tissue-type plasminogen activator concentration and decrease in plasma fibrinogen concentration.[10] These mechanisms partly overlap statins pleiotropic effects and it is unknown if alcohol benefits in cardiovascular disease occur in patients under treatment with statins.

At the present, the cardiovascular benefits and risks of alcohol consumption have been interpreted based on data from observational studies, and there is still a considerable ambiguity, as multiple lifestyle and cardiovascular risk factors are known confounders between alcohol intake and outcomes. The ARIC database presents a unique opportunity to assess the effect of alcohol consumption on heart failure in a population of Caucasians and African-Americans with records of alcohol consumption pattern during the last 25 years. Our aim will be to assess the protective effect of alcohol for HF in this cohort and establish the cut-off limit for the beneficial amount of alcohol per year according to sex and race.

5. Main Hypothesis/Study Questions:

This study will prospectively assess the relation between alcohol consumption and the risk of heart failure in the ARIC cohort.

1. Mild to moderate alcohol consumption is associated with lower incidence of heart failure both in Caucasians and in African Americans

2. Mild, but not moderate alcohol consumption is associated with lower incidence of heart failure in woman
3. The beneficial effects of alcohol are dependent of the amount of alcohol consumed per week/month and independent of the type of beverage
4. Mild to moderate alcohol consumption has no protector effect for HF in patients under long-term treatment with statins.

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 from visit 1 and V5 outcome results on HF. Participants will be excluded if they have previous history of HF at baseline, who were neither White nor African American and with inadequate measures of alcohol intake or with missing data for covariates utilized in the analysis. In order to minimize the confounder effect of coronary artery disease we will adjust the analyses using incident myocardial infarction as a time-varying covariate.

Variables to be evaluated

Dependent variables:
Outcome: heart failure (defined as the first occurrence of either a hospitalization that included an International Classification of Diseases, 9th Revision (ICD-9) discharge code of 428 (428.0 to 428.9) among the primary or secondary diagnoses or else a death certificate with an ICD-9 code of 428 or an ICD-10 code of I50 among the listed or underlying causes of death).
In secondary analyses, we will also consider cardiac biomarkers of heart failure (NT-proBNP and high sensitivity troponin T).

The independent variables 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. 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), incident acute myocardial infarction (time varying covariate), use of antihypertensive medications or statins, plasma lipid levels (i.e. HDL and LDL cholesterol, apolipoprotein AI and B, triglycerides) and clotting factors.

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. The differences in the crude incidence of HF will be also compared with chi-square tests. Separate analysis on the toxic effect

and the protective effect of alcohol consumption and incident of HF will be performed using Cox proportional hazards model. We will create a univariate and a multivariate model to identify both the unadjusted and adjusted risk of the outcome of interest. The multivariate model will include the potential confounders: demographic characteristics, cardiovascular risk factors, use of antihypertensive medications or statins, plasma lipid levels and clotting factors. Incident myocardial infarction will be introduced in the analysis as a time varying covariate. Two-sided values of p> 0.05 will be considered significant.

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

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)?

Previous studies regarding this subject have been performed in this cohort, but none assessed the longest time of follow-up, neither the cut-off values for potential benefit in alcohol consumption nor the use of statins.

Alcohol consumption and incident CHD, CVD and total mortality # 449
Alcohol consumption and risk of congestive heart failure # 922
Heart failure incidence and survival: 13 year follow up of the ARIC cohort # 927

Changing in alcohol consumption pattern and risk of incident CHD# 1023r
The heart failure population burden due to acquired risk factors: The Atherosclerosis Risk in Communities study # 1570

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. 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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