ARIC Manuscript Proposal #2229

PC Reviewed: 9/10/13  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Alcohol consumption and left atrial size and function

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

2. Writing Group:
Writing group members: Alexandra Gonçalves, Pardeep S. Jhund, Amil M Shah, Laura Loehr, 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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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 and may protect against the development of heart failure (HF). Established alcoholic cardiomyopathy is characterized by pronounced left atrial (LA) and LV dilatation, thin LV walls and significant systolic impairment at the symptomatic phase but, the earlier stage of cardiac dysfunction by alcohol consumption has been poorly addressed. Moreover, alcohol consumption is known to increase the risk of atrial fibrillation, and heavy alcohol consumption has been associated with increased risk for paroxysmal atrial fibrillation (so-called “holiday heart syndrome”).

However, it has been described that heavier alcohol consumption is associated with increase in left atrial volume in patients with coronary artery disease. Left atrial enlargement is a robust predictor of cardiovascular outcomes in the general population and a marker of poor prognosis in patients with various cardiovascular diseases. It has been described an independent association between LA volume and incidence and prevalence of systolic and diastolic HF. Moreover, LA function, has been recognized as an independent predictor of HF hospitalization in subjects with coronary heart disease and preserved baseline LV ejection fraction, and it has been suggested as a marker of LV diastolic function.

*Whether left atrial size or function is affected by moderate or heavy alcohol consumption in patients without left ventricular dysfunction is unknown.*

It is likely that currently genetic factors contribute to the susceptibility to alcoholic cardiomyopathy. 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. 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) untitled” 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 propose to assess the effect of alcohol consumption on left atrial size and function, by assessing the effect on LA size and function. We propose to investigate if patients with moderate-to heavy alcohol consumption present LA dilatation or low LA ejection fraction.
as an earlier stage of alcoholic cardiomyopathy, and whether this is modified by alcohol-metabolizing genes.

5. Main Hypothesis/Study Questions:

1. Moderate-heavy alcohol consumption is associated with LA dilatation assessed by 2D or 3D volumes quantification
2. Moderate-heavy alcohol consumption is associated with reduced LA ejection fraction assessed by 2D or 3D volumes quantification
3. Mild alcohol consumption has no significant effect in LA ejection fraction.
4. LA dilatation and ejection fraction impairment among alcohol consumers is modified 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 or atrial fibrillation 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 atrial maximum and minimum volumes, LA ejection fraction evaluated by 2D or 3D measurements. In secondary analyses, we will also consider 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, incidence of atrial fibrillation, 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 (LA volumes and ejection fraction) 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 or atrial fibrillation, 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 LA volumes and ejection fraction 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?

_X__ 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.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)?
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?
   _X_ Yes  ___ No

11.b. If yes, is the proposal
   ___   A. primarily the result of an ancillary study (list number* __________)
   _X_  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 shows you which journals automatically upload articles to Pubmed central.

References


10. Gottdiener JS, Kitzman DW, Aurigemma GP, Arnold AM, Manolio TA. Left atrial volume, geometry, and function in systolic and diastolic heart failure of persons > or =65 years of age (the cardiovascular health study). The American journal of cardiology. 2006;97:83-89


