ARIC Manuscript Proposal #2535

PC Reviewed: 6/9/15      Status: A      Priority: 2
SC Reviewed: _________      Status: _____      Priority: ____

1.a. Full Title: Liver injury in alcohol drinkers and incidence of heart failure. The ARIC study.

1.b. Abbreviated Title: Alcoholic liver injury and heart failure

2. Writing Group:
Writing group members: Odilson Marcos Silvestre, Alexandra Gonçalves, Gabriela Querejeta Roca, Brian Claggett, Chiadi E. Ndumele, Mariana Lazo, Scott D. Solomon, others welcome.

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

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3. Timeline: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months.
4. Rationale:
The association between alcohol consumption and incident heart failure (HF) has already been demonstrated. However, it is not properly known which factors are related to a higher risk of HF among alcohol drinkers. The quantity of alcohol intake has been considered the main factor in the association between alcohol consumption and HF. Heavy intake is related to development of cardiomyopathy, while light-moderate intake has been shown to have a protective effect. Nevertheless, studies in this field have demonstrated conflicting results in terms of the amount of alcohol consumed and duration of alcohol abuse that might be related to incident HF. It is likely that in addition to the quantity of ethanol and sex-specific susceptibility, other important factors such as genetic susceptibility, metabolic factors and presence of comorbidities could interact to increase the risk of HF. Furthermore, the estimation of quantity of alcohol is inaccurate because as it is derived from questionnaires with self-reported alcohol intake, it tends to be underreported, especially among heavy drinkers. Then, there are no reliable markers to identify people at risk of HF between alcohol drinkers.

The liver is more vulnerable to alcohol damage than the heart. About 10g of alcohol per day for women and 20g per day for men have been associated with liver damage and may lead to cirrhosis. Cytokine production by Kupffer cells, reactive oxygen species produced by direct alcohol effect, and activated macrophages have been described as different potential pathways involved in the development and progression of liver disease. The inflammation activity related to alcoholic liver injury may induce damage in remote organs, such as the heart, increasing the prevalence of cardiovascular disease. Consequently, more than a shared organic propensity to cell damage by alcohol between liver and heart, it is possible that additional mechanisms might increase the incidence of HF after alcohol-related liver injury. Considering that alcohol toxicity in the liver is presented earlier than heart toxicity, markers of liver damage might predict incident HF.

Liver damage is conventionally diagnosed by the detection of high levels of liver enzymes, being aspartate aminotransferase (AST) and alanine aminotransferase (ALT) the main markers of hepatocellular injury. In addition, alkaline phosphatase and gamma glutamyl transferase (GGT) are markers of liver injury and cholestasis. Specifically, the combination of AST:ALT ratio greater than 2 and elevated GGT accurately detects alcohol-related liver injury.
Currently, it is unknown if patients who develop liver injury related to alcohol abuse have an increased risk of heart failure. In consequence, we sought to analyze the association between alcohol-related liver damage and incident heart failure.

**Aim:**

To evaluate the association between alcohol-induced liver injury and incidence of heart failure in the population of the ARIC study.

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

Among alcohol drinkers, the presence of liver damage is associated to a higher risk of incident heart failure.

**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 methodological limitations or challenges if present).**

**Study Design and Inclusion/Exclusion Criteria:**

We will perform an analysis of alcohol-related liver damage, defined by the liver enzymes levels at Visit 4 and evaluate its association with heart failure and death. The study sample will include patients who are current alcohol drinkers and who had measured the liver enzymes levels (ALT, AST and GGT) in Visit 4 (1987-1989). The current drinkers will be compared with former drinkers and never drinkers regarding the association between alcohol-related liver damage and risk of heart failure. We will exclude patients with liver disease (cirrhosis and hepatitis) and heart failure diagnosed at Visit 4.

**Variables to be evaluated**

**Exposures variables:**

1) ALT, AST and GGT serum levels evaluated as continuous variable after being log-transformed to assess the association with HF.

2) ALT, AST and GGT categorized as normal range or elevated as previously defined in ARIC study.\(^{11}\)

3) AST:ALT ratio categorized in >2 and \(\leq 2\).

**Outcome variables:**

Incident heart failure and all cause mortality.
Potential covariates:
Demographic characteristics (age, race, sex, body mass index, ARIC center), cardiovascular risk factors (arterial hypertension, dislipidemia, alcohol consumption, smoking status, LDL-C, HDL-C), blood pressure, use of antihypertensive medications or statins, glucose, plasma lipid levels (i.e. HDL and LDL cholesterol, triglycerides), and creatinine clearance.

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. We will use natural log-transformed values for the liver enzymes to normalize the distribution in the population. Liver enzymes will be analyzed as log-transformed continuous and dichotomous using laboratory defined cut-points. Categorical data will be reported as percent frequencies and compared by chi-squared or Fischer exact tests. Continuous data will be compared by Wilcoxon rank sum test, t test, Kruskall-Wallis test and 1-way ANOVA followed by Bonferroni test as appropriate. Analysis on the effect of liver damage (elevated ALT, AST, GGT and AST: ALT>2) in the incidence of heart failure and death will be performed using Cox proportional hazards model. We will create a univariate and a multivariable model to identify both the unadjusted and adjusted risk of the outcome of interest. The multivariable model will include the potential confounders: age, sex, race, body mass index, ARIC center, arterial hypertension, dislipidemia, amount of alcohol consumption, smoking status, statins’ use, creatinine clearance and coronary heart disease. P-values <0.05 will be considered significant.

Limitations:
A limitation of this study is that liver enzymes are the only marker of alcohol-related liver injury available. Ideally, liver biopsy or an image-based marker of liver injury would improve the accuracy of alcohol-related liver damage. In addition, other prevalent conditions as nonalcoholic steatohepatitis and hepatitis C can cause enzyme alterations regardless the alcohol effect.

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)?

1-Non-Alcoholic Fatty Liver Disease and the Risk of Incident Cardiovascular Disease: The Atherosclerosis Risk in Communities (ARIC) Study
Manuscript Proposal # 1833
Authors: Chiadi E. Ndumele; Andrea Christman; Mariana Lazo; Jeanne Clark; Ron C. Hoogeveen; Roger S. Blumenthal; Josef Coresh; Elizabeth Selvin.

2- Elevated Liver Enzymes and Risk of Diabetes
Manuscript Proposal # 1789
Authors: James Pankow; Bruce Duncan; Maria Ines Schmidt; Christie Ballantyne; Ron Hoogeveen; Laura Rasmussen-Torvik; Heejung Bang; Jeanne Clark

3- Liver Enzyme Activity and Risk of Diabetes
Manuscript Proposal # 977
Authors: Andrea Christman; Lazo; Ndumele; Clark; Coresh; Selvin; Pankow

4- Alcohol consumption and risk of heart failure
Manuscript Proposal #2247
Authors: Alexandra Gonçalves, Pardeep S. Jhund, Brian Claggett, Wayne Rosamond, Anita Deswal, David Aguilar, Amil M Shah, Susan Cheng, Scott D. Solomon

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)* #946)

*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.

References:


