ARIC Manuscript Proposal #2442

PC Reviewed: 9/9/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Alcohol consumption and myocardial biomarkers

b. Abbreviated Title (Length 26 characters): Alcohol consumption, hs-cTnT and NT-proBNP.

2. Writing Group:

Writing group members: Mariana Lazo; Yuan Chen; John W. McEvoy; Chiadi Ndumele; Suma Konety; A. Richey Sharrett; Christie M. Ballantyne; Elizabeth Selvin; others welcome

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

First author: **Mariana Lazo, MD, PhD**
Address: Department of Epidemiology
Welch Center for Prevention, Epidemiology & Clinical Research
Johns Hopkins School of Public Health
2024 E. Monument St. Suite 2-600
Baltimore, MD 21287
Phone: 410-614-4096. Fax: 410-955-0476
E-mail: mlazo@jhsph.edu

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).

Name: Elizabeth Selvin, PhD, MPH
Address: Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Welch Center for Prevention, Epidemiology, and Clinical Research
2024 E Monument Street, 2-600
Phone: 410-614-3752 Fax: 410-955-0476
E-mail: lselvin@jhsph.edu

3. Timeline: We aim to submit this paper for ARIC review <1 year from approval of the manuscript proposal

4. Rationale:

Epidemiologic studies have demonstrated a beneficial effect of low and moderate alcohol consumption on cardiovascular disease, in particular on coronary artery disease morbidity and mortality.[1] However, there are also numerous adverse consequences of alcohol consumption [2-4] that may offset beneficial effects and that make it difficult to provide clinical recommendations regarding regular alcohol consumption.

To better understand the cardiovascular effects of alcohol consumption, it is important to examine the effects of different amounts and patterns of alcohol consumption on subclinical cardiac disease. The literature reporting the association between alcohol consumption and subclinical cardiovascular disease is scarce. Few studies have examined the association between alcohol consumption and atherosclerosis, and the results have been inconsistent. In the MESA study, alcohol consumption was not associated with prevalence of coronary atherosclerosis as assessed by coronary artery calcium, except for those with binge drinking (RR 1.12, 95% CI 1.03-1.17)[5]. An analysis of ARIC data[6] showed a null association with markers of subclinical atherosclerotic disease including carotid intima medial thickness. In contrast, there are studies that suggest a beneficial effect of moderate drinking. In one study, compared to never drinkers, those with moderate consumption of alcohol were significantly less likely to have extensive coronary calcification[7]. In another study of middle aged women with existing coronary heart disease, those with moderate consumption had less progression of angiographically-measured coronary atherosclerosis[8].

Beyond the effects on atherosclerosis or atherosclerotic risk factors[9], the effects of alcohol on the myocardium are unclear. Novel cardiac biomarkers tests can detect subclinical myocardial damage and hemodynamic stress.

Cardiac Troponin-T (cTnT), a measure of myocardial damage, is associated with cardiovascular disease outcomes in both the general population and in high-risk groups[29]. New high sensitivity assays for cardiac troponin-T (hs-cTnT) have much lower detection limits than standard clinical cTnT assays [30] and have also been shown to improve the prediction of cardiovascular morbidity and mortality in subjects with stable coronary artery disease [31] and in persons without clinically evident cardiovascular disease in ARIC [32]and other population-based cohorts[33, 34].

B-type natriuretic peptide is closely associated with left ventricular mass index[35] and is clinically used for heart failure diagnosis and prognosis[36]. N-terminal pro-brain natriuretic peptide (NT-proBNP) is also associated with cardiovascular risk [37] and mortality[38, 39]. When compared to BNP, NT-proBNP was superior in the prediction of death in the general population [40]. NT-proBNP has been demonstrated to detect subclinical left ventricular dysfunction [42].

The availability of both novel assays of cardiac biomarkers at two time points (6 years apart) in ARIC offers an opportunity to extend previous ARIC findings[10-14] and rigorously characterize the associations of alcohol with subclinical myocardial damage and hemodynamic stress. In addition, the ARIC study offers other important advantages

such as its large size, thorough characterization of potential confounders and repeated measures of alcohol consumption.

We seek to investigate the relationship of average alcohol consumption, patterns of alcohol consumption (binge, frequency, amount and changes) with biomarkers of myocardial damage and structural heart disease.

5. Main Hypothesis/Study Questions:

Study Question 1: What is the cross-sectional, independent, association of alcohol consumption (amount and frequency) with hs-cTnT and NT-proBNP?
Study Question 2: What is the prospective, independent, association of alcohol consumption (amount and frequency) with incident subclinical myocardial damage, as defined by 6-year risk of elevation in hs-cTnT?
Study Question 3: Are there different associations (cross-sectional or prospective) by race, sex, type of alcohol consumed (wine, beer, liquor) and pattern of alcohol use (binge vs non-binge)?

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: The study has a cross-sectional and a prospective component.

Cross-sectional: We will examine the association of alcohol consumption with cardiac biomarkers (hs-cTnT and NT-proBNP) at ARIC visit 2.

Prospective: We will examine the association of baseline [ARIC visit 2 (1990-1992)] and change in alcohol consumption with 6 year changes in hs-cTnT and NT-proBNP [ARIC visit 4 (1996-1998)]

Exposure:
The following alcohol related (or surrogates) data are available in ARIC:

Variables	V1	V2	V3	V4
Summary ethanol intake per week (grams)	X	X	X	X
Current status: current, former, never	X	X	X	X
If former: Number of years since quitting	X	X	X	X
If former: Number of years drinking	X	X	X	X
If former: Type of drinks and average number of drinks	X	X	X	X
Usual number of glasses of wine, beer and liquor per week (asked separately)	X	X	X	X
Past 24 hrs: drinks, wine, beer, liquor (amount-units)	X	X	X	X
Frequency per week per type of drink			X	X
Binge			X	
GGT		X		X
HDL	X	X	X	X

For each of the visits, for current drinkers, we will use the number of drinks per week to categorize them into groups: ≤1, 2-3, 4-5,6-7, 8+, drinks per week. We will additionally examine commonly used cut-points of what has been considered excessive alcohol consumption: >14 drinks/week in men and >7 drinks/week in women (mostly used in the US)[15]; and >21 drinks/week in men and >14 drinks/week in women (mostly used outside the US)[16].

We will explore the changes in alcohol consumption (status and ethanol intake volume) across visits. If, as we hypothesize, the status of consumption is stable over time we will use the information regarding frequency and binging only available at visit 3 to impute visit 2.

Furthermore, based on the changes in alcohol consumption we will create categories to reflect decrease, increase and no change.

Outcomes:
Hs-cTnT will be examined continuously and categorically based on other existing ARIC literature (e.g., <5, 5-8, 9-13 and ≥14 ng/L)[17].

NT-proBNP will be analyzed both categorically and as a continuous variable. For the categorical analyses it will be categorized into: undetected, quartile 1, 2, 3 and 4.

Changes in hs-cTnT will be analyzed continuously and categorically (incident elevated [≥14 ng/L]) based on other existing ARIC literature[17].
Changes in NT-pro BNP will be analyzed continuously and categorically (incident elevated [≥300][18])

Exclusions:

We will exclude individuals with ethnicity other than black or white, those with missing alcohol consumption information or implausible [>4 SD] levels of alcohol consumption, those with missing hs-cTnT, NT-proBNP or missing covariates of interest and those individuals with existing CHD or CHF at visit 2.

Statistical analyses:
We will use linear and logistic regression models to assess the cross-sectional association between alcohol consumption (status, amount and frequency) and hs-cTnT and NT-proBNP at Visit 2). Multinomial regression models will be used to estimate odds ratios and their 95% CIs for elevated hs-cTnT or NT-proBNP, by the categories of alcohol consumption and to account for intervening CVD, CHF events or deaths between visit 2 and 4. Different reference groups (e.g. never, low) will be used to examine the robustness of the findings. For analyses of amount of alcohol we will adjust for frequency and viceversa). In addition, among current drinkers, we plan to model the association between

alcohol amount and hs-cTnT and NT-proBNP using restricted cubic splines to better characterize the shape of the potential associations.

All multivariable models will be adjusted for age (years), race-center (whites-Washington County; whites-Minneapolis; blacks-Jackson; blacks-Forsyth County, whites-Forsyth County), sex (male or female), body mass index (kg/m2), C-reactive protein (mg/L), smoking (current; former; never), LDL-cholesterol (mg/dL), triglycerides (mg/dL), diabetes (yes or no); current use of cholesterol-lowering medication (yes or no); estimated glomerular filtration rate (mL/min/1.73m2); and left ventricular hypertrophy (yes or no).

A separate model will be used to additionally adjust for mean systolic blood pressure (mm Hg), current use of hypertension medication (yes or no), and HDL-cholesterol (mg/dL) as they may be mediators of the alcohol effects.

We will formally test the presence of race- or sex- interactions and will present the results stratified if statistically significant.

Secondary analyses:
In secondary analyses we will explore the effects of amount of alcohol consumption on cardiac biomarkers by predominant (>60%[11, 12]) type of alcoholic beverage.
In addition, the role of binging on cardiac biomarkers will be examined separately.
Given that blood pressure may be an important effect modifier, we will conduct sensitivity analyses stratifying by hypertension status and we will formally test for interaction.
Sensitivity analyses will be conducted adjusting for baseline levels of the biomarkers and adjusting for each other.

Limitations:

We will be using self-reported alcohol consumption to classify individual's exposure status, thus there is the possibility of misclassification and reporting bias, in particular among heavy drinkers.
There may be limited power to examine the association between heavy and binge drinking and cardiac biomarkers. Only 10% of the participants reported at visit 3 ever drinking 5 or more drinks per day and similarly a low prevalence of heavy alcohol consumption in this population has been reported. Similarly, we will have limited power to evaluate the association between specific type of alcoholic beverage and cardiac biomarkers.
For examining drinking patterns (binging) we will be relying on information obtained at visit 3 and we will classify individuals as "ever bingers".

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 ICTDER 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)?

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* 2009.16 and 2008.10)
___ 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.

References

1. Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: A systematic review and meta-analysis. *BMJ*. 2011;342:d671. doi: 10.1136/bmj.d671.:d671
2. Room R, Babor T, Rehm J. Alcohol and public health. *Lancet*. 2005;365:519-530
3. Ballester M, Marti V, Carrio I, Obrador D, Moya C, Pons-Llado G, Berna L, Lamich R, Aymat MR, Barbanoj M, Guardia J, Carreras F, Udina C, Auge JM, Marrugat J, Permanyer G, Caralps-Riera JM. Spectrum of alcohol-induced myocardial damage detected by indium-111-labeled monoclonal antimyosin antibodies. *Journal of the American College of Cardiology*. 1997;29:160-167
4. Djousse L, Gaziano JM. Alcohol consumption and heart failure: A systematic review. *Current atherosclerosis reports*. 2008;10:117-120
5. McClelland RL, Bild DE, Burke GL, Mukamal KJ, Lima JA, Kronmal RA, Multi-Ethnic Study of A. Alcohol and coronary artery calcium prevalence, incidence, and progression: Results from the multi-ethnic study of atherosclerosis (mesa). *Am J Clin Nutr*. 2008;88:1593-1601
6. Demirovic J, Nabulsi A, Folsom AR, Carpenter MA, Szklo M, Sorlie PD, Barnes RW. Alcohol consumption and ultrasonographically assessed carotid artery wall thickness and distensibility. The atherosclerosis risk in communities (aric) study investigators. *Circulation*. 1993;88:2787-2793
7. Vliegenthart R, Oei HH, van den Elzen AP, van Rooij FJ, Hofman A, Oudkerk M, Witteman JC. Alcohol consumption and coronary calcification in a general population. *Archives of internal medicine*. 2004;164:2355-2360
8. Janszky I, Mukamal KJ, Orth-Gomer K, Romelsjo A, Schenck-Gustafsson K, Svane B, Kirkeeide RL, Mittleman MA. Alcohol consumption and coronary atherosclerosis progression--the stockholm female coronary risk angiographic study. *Atherosclerosis*. 2004;176:311-319
9. Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: Systematic review and meta-analysis of interventional studies. *BMJ*. 2011;342:d636. doi: 10.1136/bmj.d636.:d636
10. Eigenbrodt ML, Fuchs FD, Hutchinson RG, Paton CC, Goff DC, Jr., Couper DJ. Health-associated changes in drinking: A period prevalence study of the atherosclerosis risk in communities (aric) cohort (1987-1995). *Prev.Med.* 2000;31:81-89
11. Fuchs FD, Chambless LE, Folsom AR, Eigenbrodt ML, Duncan BB, Gilbert A, Szklo M. Association between alcoholic beverage consumption and incidence of coronary heart disease in whites and blacks: The atherosclerosis risk in communities study. *Am J Epidemiol*. 2004;160:466-474
12. Fuchs FD, Chambless LE, Whelton PK, Nieto FJ, Heiss G. Alcohol consumption and the incidence of hypertension: The atherosclerosis risk in communities study. *Hypertension*. 2001;37:1242-1250
13. Volcik KA, Ballantyne CM, Fuchs FD, Sharrett AR, Boerwinkle E. Relationship of alcohol consumption and type of alcoholic beverage consumed with plasma

lipid levels: Differences between whites and african americans of the aric study. *Ann.Epidemiol.* 2008;18:101-107
14. Eigenbrodt ML, Mosley TH, Jr., Hutchinson RG, Watson RL, Chambless LE, Szklo M. Alcohol consumption with age: A cross-sectional and longitudinal study of the atherosclerosis risk in communities (aric) study, 1987-1995. *Am J Epidemiol*. 2001;153:1102-1111
15. NIAAA.
16. WHO/Europe. European status resport on alcohol and health. 2010
17. Selvin EL, M.; Chen, Y.; Shen, L.; Rubin, J.; McEvoy, J.W.; Hoogeveen, R.C.; Sharrett, A.R.; Ballantyne, C.M.; Coresh, J. Diabetes, pre-diabetes and incidence of subclinical myocardial damage. *Circulation*. 2014
18. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, Pinto YM, Richards M. Nt-probnp testing for diagnosis and short-term prognosis in acute destabilized heart failure: An international pooled analysis of 1256 patients: The international collaborative of nt-probnp study. *European heart journal*. 2006;27:330-337