ARIC Manuscript Proposal #2902

PC Reviewed: 12/13/16	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Homocysteine, B Vitamins and Incident Atrial Fibrillation: the Atherosclerotic Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Homocysteine, vitamin B and AF

2. Writing Group:

Writing group members: Yasuhiko Kubota, Alvaro Alonso, Faye Norby, Aaron Folsom, others welcome

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

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3. Timeline:

Data analysis: 1-2 months from manuscript approval date.
First draft of the manuscript: 2-3 months from manuscript approval date.

4. Rationale:

Observational studies have suggested elevated levels of homocysteine in the general population are associated with an increased risk of cardiovascular diseases (CVD) such as coronary heart disease, heart failure and stroke (1–4). While several randomized controlled trials have suggested no protective effect on CVD risk of lowering plasma homocysteine levels with vitamin B supplements (5–9), previous meta-analyses of

clinical trials have reported vitamin B supplementation for homocysteine reduction significantly reduced stroke events (10, 11). Thus whether or not homocysteine is a causal risk factor for CVD in the general population remains somewhat unclear. In any case, elevated levels of homocysteine can be considered at least to be a risk marker for CVD.

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia encountered in Western countries, and millions of individuals are expected to suffer from it in the next decades (12). Thus, it is important to identify individuals at high risk of developing AF. Several risk factors for AF have been so far identified (13). However, few studies have investigated the association between homocysteine and AF risk (14, 15). Homocysteine may be expected to be related to AF risk, considering the close relations between homocysteine and atherosclerotic CVD risk. A case-control study indicated patients with AF had both elevated homocysteine levels and decreased vitamin B6 levels (14) while a prospective study showed no significant association (15).

Therefore, we sought to test the hypothesis that elevated levels of homocysteine are associated with increased incident AF risk independent of other AF risk factors, using data from ARIC's previous nested case-cohort studies.

5. Main Study Questions:

Elevated levels of homocysteine are associated with increased incident AF risk independent of other AF risk factors. We also will explore a possible inverse association of B vitamin intake and AF incidence.

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).

Design

Prospective cohort

Inclusion/exclusion criteria

Inclusion: Participants who provided blood samples for homocysteine and B vitamins at visit 1 (n=about 800). There were measured in nested case-cohort studies of CVD cases in 1-3, so the analysis must take into account the original sampling strata.

Exclusion: Those who had prevalent AF at visit 1.

Main exposure

Plasma homocysteine levels and B vitamin (B6, B12, and folate) at visit 1.

Covariates

Age, sex, race/ARIC field center, body mass index, sitting height, systolic and diastolic blood pressure, anti-hypertension medication, diabetes mellitus, estimated GFR, smoking status, alcohol drinking, left ventricular hypertrophy by ECG, prevalent heart failure at visit 1, as well as time-varying CVD (coronary heart disease and heart failure).

Endpoints
Incident AF from visit 1 through 2,013.

Statistical analysis
Firstly, covariates first will be presented according to tertiles (or quartiles) of plasma homocysteine levels.

Secondly, hazard ratios and their 95% confidence intervals for incident AF will be calculated using a weighted Cox proportional hazard models in relation to tertles of plasma homocysteine levels and 1-SD increment for natural log-transformed or log_2-transformed plasma homocysteine levels if we find homocysteine is left or right skewed for early coronary heart disease cases (n=about 250) and a cohort random sample (n=about 550), respectively.

- Model 1: adjustment for age, sex, race, and ARIC study site.
- Model 2: Model 1 + adjustment for baseline body mass index, sitting height, systolic and diastolic blood pressure, anti-hypertension medication, diabetes mellitus, estimated GFR, smoking status, alcohol drinking, left ventricular hypertrophy by ECG, and prevalent heart failure.
- Model 3: Model 2 + adjustment for time-varying CVD.

Lastly, similar analyses above in relation to plasma vitamin B6, B9 (folic acid) and B12 will be conducted.

- Model 1: adjustment for age, sex, race, ARIC study site and case-cohort status.
- Model 2: Model 1 + adjustment for baseline body mass index, sitting height, hypertension, diabetes mellitus, estimated GFR, smoking status, alcohol drinking, left ventricular hypertrophy by ECG, and prevalent heart failure
- Model 3: Model 2 + adjustment for time-varying CVD.

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)?

Multiple ARIC papers on individual outcomes. For example:

#228: Homocysteine and IMT progression
#389: Associations of homocystein with incident CHD and MRI stroke (PMID: 9697819)
#857: Plasma Vitamin B6 and Inflammation Markers (PMID: 12860264)

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* 2006.16)
___ 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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

References:

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