ARIC Manuscript Proposal # 3055

PC Reviewed: 10/3/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Association of antidepressant medications with the risk cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study.

b. Abbreviated Title (Length 26 characters): **Antidepressants and CVD risk**

2. Writing Group:

Writing group members: Zakaria Almuwaqqat, Wesley T O'Neal, Amit J Shah, Viola Vaccarino, J Doug Bremner, Lin Y. Chen, Pamela L. Lutsey, Amanda Seyerle, Alvaro Alonso, others welcome.

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

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3. Timeline:

September 2017 – Submit proposal
Oct- January 2017 – Data analysis/Manuscript preparation
January-Feb 2017 – Submit manuscript for P&P review

4. Rationale:

Antidepressant medications are among the most commonly prescribed medications for U.S. adults. Although these medications are effective against depression, which is an established cardiovascular disease (CVD) risk factor, their relationship with CVD risk independently of depression is not clear [1-3]. A few population-based observational studies indicated an increased risk of stroke, atrial fibrillation (AF) and CV events associated with selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCA) [4, 5]. For example, Jerrel et al have found that among children and adolescents, patients who were exposed to SSRIs and weight-inducing antidepressants had a higher risk for incident cardiovascular events [6]. In contrast, other studies have demonstrated protective effects for ADs against CVD risk. Santangelo et al have shown that sertraline and citalopram are associated with reduction in CVD events [7]. Similarly, in depressed patients who experienced an acute Myocardial Infarction (MI), Taylor et al have reported that the use of SSRIs might reduce subsequent cardiovascular morbidity and mortality [8]. Furthermore, Zuidersma et al reported that among post MI patients, antidepressant use was associated with improved survival even though it was not related to CVD risk [9].Other studies have shown that TCA as compared to SSRI might be associated with excess CVD risk [10, 11].

We have shown previously that antidepressants are associated with amelioration of P Terminal Force in V1 (PTFV1) changes during mental stress (abstract to be presented during AHA Scientific Sessions 2017). Given that PTFV1 is a known marker for AF, stroke and heart failure (HF) [12, 13], our findings were suggestive of a possible protective effect of antidepressants on the risk of AF, stroke and HF. Therefore, we seek to study the association of antidepressant medications with the risk of CVD in the community using the ARIC study. CVD events will be defined as incident MI, HF, AF, stroke, and CV mortality. Because depressive symptoms and life time depression diagnosis have not been systematically assessed in ARIC during follow up, we will obtain relevant hospitalization ICD-9 codes regarding the diagnosis of depression and PTSD, and will use data from the Maastricht Vital Exhaustion Questionnaire administered at Visit 2 as an imperfect proxy for depressive symptoms.

5. Main Hypothesis/Study Questions:

1) AD use is associated with reduced risk of CVD (defined as MI, HF, AF, stroke, and CV mortality) as compared to participants not taking ADs.

2) SSRI antidepressants use is associated with reduced risk of CVD as compared to non-SSRI antidepressants.

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 participants

Eligible participants will be from the ARIC cohort (n=15,792) with baseline examination data. We identified 1400 participants in ARIC who reported using antidepressant in at least one of the first 4 visits (between 1987-89 and 1996-98).

Exclusion criteria
Prevalent CVD (defined as MI, HF, AF, or stroke) at baseline will be excluded.

Main exposure
Antidepressants: Tricyclic antidepressants (TCA) or Selective serotonin inhibitors (SSRI) or all other antidepressants combined, as assessed by medication inventory during study visits.

ADs users: participants in the ARIC study who reported using antidepressant (SSRI or TCA or other) in at least one of the 4 visits (between 1987-89 and 1996-98). We will also perform separate analyses in those using ADs comparing different types of AD (SSRI vs TCA vs others).

Outcome definition
CVD
The primary endpoint will be a composite of HF, MI, stroke, AF or CV-related death. We will also consider each endpoint separately.

- HF, non-fatal MI, and stroke will be defined based on adjudicated cases following standard ARIC definitions.
- CV-related death will be considered if the underlying cause of death was a CVD (ICD-9 390-459 or ICD-10 I00-I99).
- AF will be defined as in previous ARIC analyses using study ECGs, ICD-9 code 427.31 or 427.32 in the discharge codes in the absence of open heart surgery, or AF listed as a cause of death.

The incidence date of CVD will be defined as the date for the first CVD diagnosis or the date of out of hospital death if that's the first manifestation of CVD. Follow-up will be available through the end of 2014.

Other Variables of Interest
Demographic - Age, Race, Sex, Education, Clinic site
Comorbidities – Dementia, Diabetes, systolic and diastolic blood pressure, use of antihypertensive medication, HDLc, LDLc, use of lipid-lowering medication
Others – Alcohol consumption, smoking, body mass index, vital exhaustion at visit 2, depression (based on ICD-9 codes 296.2- 296.3 and 311), PTSD and acute stress disorder (based on ICD-9 codes 309.81 and 308.3)

Analysis plan

Eligible participants not meeting any of the exclusion criteria above will be part of the study analysis.

1) Comparison of baseline characteristics
   Participants will be compared according to antidepressants use (ADs) (ADs vs non-ADs).

2) Associations of AD with incident CVD
   Hazard ratios (HRs) for incident CVD (and separately for each endpoint) will be calculated for those who were exposed to ADs compared to those who were not exposed to ADs. We will also repeat the analysis restricted to participants using ADs and comparing different types of AD.

Multivariable Cox proportional hazards model for CVD risk with time-dependent AD use as the primary exposure with adjustment for demographics, clinical comorbidities including traditional CV risk factors will be used to compute HRs and 95% confidence intervals (CI) for the abovementioned associations between ADs and incident AF, overall and stratified by race and sex. Depression and PTSD diagnoses based on ICD codes will also be included as time-dependent covariates. We will evaluate non-CVD deaths in secondary analyses—this will allow us to see if there are important other causes of death potentially causing competing risks.

We will evaluate the effect modification by race and sex using stratification and comparing models with and without interaction terms

Limitations

Major limitations of this analysis include the information on AD use being restricted to clinic visits and the lack of detailed information on depressive symptoms and a diagnosis of depression. The later point will be partly addressed by using hospital diagnoses and information on vital exhaustion collected at visit 2.

7.a. Will the data be used for non-CVD analysis in this manuscript? 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? 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.** cARIC 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

   No overlap with existing proposals

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? 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.

13. Per Data Use Agreement Addendum, approved manuscripts using 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 No

References:

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