1.a. Full Title:

Association of antidepressant type 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:


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]

First author: Zakaria Almuwaqqat
Address: Dept of Medicine
Emory University School of Medicine
1354 Clifton Rd
Atlanta, GA 30322
Phone: 203-824-7207
E-mail: zalmuwa@emory.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: Alvaro Alonso
Address: Dept of Epidemiology, Rollins School of Public Health
Emory University
1518 Clifton Rd NE, CNR 3051
Atlanta, GA 30322
Phone: 404-727-8714
E-mail: alvaro.alonso@emory.edu
3. Timeline:
May 2018 – Submit proposal
June-July 2018– Data analysis/Manuscript preparation
August-September 2018– Submit manuscript for P&P review

4. Rationale:
Antidepressant medications are among the most commonly prescribed medications for US adults and their use has increased over the past two decades with changing trends in antidepressant type [1, 2]. Although these medications are effective against depression, which is an established cardiovascular disease (CVD) risk factor, their differential association with CVD risk is not clear [3-5]. A few population-based observational studies indicated an increased risk of stroke, atrial fibrillation (AF) and CV events associated with the two main types of antidepressants; selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCA) [6, 7] [8]. In contrast, other studies have demonstrated that different antidepressants types are associated with different CVD risk. For example, SSRI's are associated with a lower CVD risk. Santangelo et al have shown that sertraline and citalopram are associated with reduction in CVD events [9]. In contrast, Jerrel et al found that among children and adolescents, patients who were exposed to SSRIs and weight-inducing antidepressants had a higher risk for incident cardiovascular events. Other studies have shown that TCA as compared to SSRI might be associated with excess CVD risk [10, 11]. We propose to study the effect of SSRI use as compared to non-SSRI on CVD risk among ARIC participants who reported antidepressants use (CVD events defined as incident MI, HF, AF, stroke, and CV mortality).

5. Main Hypothesis/Study Questions:
To evaluate the association of type of antidepressant with the risk of CVD (MI, HF, AF, stroke, CVD mortality). We hypothesize that 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 reporting antidepressant use at any of the study visits (visit 1 through visit 5). We have identified >1,400 participants in ARIC who reported using antidepressant in at least one of the first 4 visits (between 1987-89 and 1996-98); this number will be higher once we include visit 5.

Exclusion criteria
Prevalent CVD (defined as MI, HF, AF, or stroke) at time of AD initiation will be excluded. Race other than white or black. Non-whites from the MN and MD centers.

**Main exposure**
Type of AD, based on self-reported information at the study visits. AD use will be categorized as SSRI, TCA or other. Participants reporting more than 1 type of AD at any particular visit will be included in the other category.

**Outcome definition**
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 is the first manifestation of CVD. Follow-up is available through the end of 2016.

**Other Variables of Interest**
Demographic - Age, Race-clinic site, Sex, Education
Comorbidities – Dementia (adjudicated by ARIC NCS, level 3 variable), 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, physical activity at baseline.

**Analysis plan**
Multivariable Cox proportional hazards model for CVD risk with time-dependent type of AD use as the primary exposure. Start of follow-up will be initiation of AD medication, end of follow up will be defined as date of CVD occurrence, December 31, 2016, or lost to follow-up, whichever occurred earlier. We will adjust for demographics, time-dependent clinical comorbidities including traditional CV risk factors. 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. SSRI exposure will be the reference group. Subjects who used SSRI and non-SSRI in the same time period will be considered as non-SSRI. Eligible participants not meeting any of the exclusion criteria above will be part of the study analysis.

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 information on vital exhaustion collected at visit 2. An additional limitation is the limited sample size to compare different ADs within any particular class.

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. 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](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/](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.cscb.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

References: