ARIC Manuscript Proposal # 3080

PC Reviewed:11/14/2017	**Status:**	**Priority: 2**
SC Reviewed:	**Status:**	**Priority:**

1.a. Full Title:
Periodontal Disease, inflammation and incidence of atrial fibrillation in the Atherosclerosis Risk In Communities (ARIC) study

b. Abbreviated Title (Length 26 characters):
PD-AF ARIC

2. Writing Group:
Writing group members:
Kolby T. Redd
Souvik Sen
Kevin Moss
Alvaro Alonso
Elsayed Soliman
Jared W. Magnani
Lin Y. Chen
Wayne D. Rosamond
James Beck
Stephen Offenbacher

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

First author: Kolby T. Redd PhD, MHA
Address: 8 Medical Park, Suite 420
Columbia, SC 29203
Phone: 803-545-6078 **Fax:** 803-545-6066
E-mail: kolby.redd@uscmed.sc.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: **Souvik Sen**
Address: 8 Medical Park, Suite 420
Columbia, SC 29203
Phone: 803-545-6073 Fax: 803-545-6066
E-mail: Souvik.sen@uscmed.sc.edu

3. **Timeline**:
Manuscript Proposal Submission: 15 November 2017
Data Acquisition: 15 December 2017
Analysis and Paper Completed: 15 January 2018

4. **Rationale**:
Previously we have reported that periodontal disease is associated with an increased risk of cardioembolic stroke. Atrial fibrillation is the most common reason for cardioembolic stroke. Thus, we propose to study the association between periodontal disease and incident atrial fibrillation as a potential mechanism for explaining the previously reported association between periodontal disease and cardioembolic stroke.

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

Is periodontal disease (PD) independently associated with increased incidence of atrial fibrillation (AF)?

Subjects with a diagnosis of PD, associated with inflammation, will have increased rates of incident AF. Is inflammation an effect modifier in PD→AF association?

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:

Inclusion/Exclusion: Visit 4 in the Dental Atherosclerosis in Communities Study (DARIC) study, participants were subjected to full-mouth clinical periodontal measurements (seven indices) collected at six sites per tooth from 6,501 subjects without prior atrial fibrillation. They were graded into seven distinct periodontal profile classes (PPC: A or periodontal health, F through G or severe disease, based on increasing extent of interproximal periodontal attachment loss. These patients were followed for AF adjudicated using electrocardiograms, hospital discharge codes, and death certificates, over the subsequent 17 years. Participants with missing dental history information and those who do not meet the criteria as above will be excluded. Subjects with prior history of atrial fibrillation will be excluded. Those with race other than whites or black will be excluded due to limited sample size.

Main exposure: PD was classified at visit 4. To identify discrete classes of individuals with PD, the following 7 tooth-level clinical parameters was used, including: ≥1 site with interproximal attachment level (IAL) ≥3mm, ≥1 site with probing depth (PD) ≥4mm, extent of bleeding on probing (BOP, dichotomized at 50% or ≥3 sites per tooth), gingival inflammation index (GI, dichotomized as GI=0 vs. GI≥1), plaque index (PI, dichotomized as PI=0 vs. Pl≥1), the presence/absence of full prosthetic crowns for each tooth, and tooth status presence (present vs. absent).

At visit 4 as participants were assessed for serum inflammatory markers including high sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), d-8-iso prostaglandin F2a (d-8-

iso), interleukin 1b (IL-1b), interleukin 1ra (IL-1ra), soluble CD14 (sCD14), Intercellular Adhesion Molecule 1(sICAM1) and tumor necrosis factor alpha (TNFa).

Main Outcome: Incident AF will be assessed by 3 methods: study ECGs, Hospital discharge codes, and death certificates. Standard, 10-second, 12-lead ECGs were obtained at baseline and at each of the subsequent follow-up examinations. Tracings were performed in the supine position using MAC PC Personal Cardiographs (Marquette Electronics Inc) and transmitted electronically to the ARIC ECG Reading Center (Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Winston Salem, North Carolina), where they underwent automated reading and coding. Tracings with AF were reviewed by a cardiologist. Incident AF was identified from hospitalizations or death certificates using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 427.31 or 427.32. (Alonso et al, 2009).

Co-variates: Age, gender, race (categorized as white and black), smoking status, alcohol use, highest level of education, coronary artery disease (CAD), congestive heart failure (CHF) adjudicated between visit 1 and 4. Body mass index was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as a systolic blood pressures of 140mmHg or higher, a diastolic blood pressure higher than 90mmHg, or use of medications to treat hypertension. Blood samples were obtained after individuals had fasted for 8 hours. Diabetes was determined by self-report of a physician diagnosis of diabetes, non-fasting blood glucose level of 200 mg/dL or higher, fasting blood glucose level of 126mg/dL or higher (to convert glucose to millimoles per liter, multiply by 0.0555), or use of insulin or other oral hypoglycemic medications. Physical activity is considered significant if performed for 4hrs/week for at least a month. Prevalent CAD was defined by electrocardiographic evidence of previous myocardial infarction (MI), history of physician diagnosed MI, or previous coronary revascularization procedure (bypass, angioplasty). Prevalent CHF was defined by the reported current intake of heart failure medication at visit 4 or evidence of manifest HF with presence of specific cardiac and pulmonary symptoms.

Statistical analysis: All participants, with or without PD, will be assessed for follow-up data on atrial fibrillation. Initially, the cumulative event-free rates for the time to incident atrial fibrillation will be estimated by the Kaplan-Meier product limit method, and the other group, PD will be compared by the log-rank test. Subsequently, the Cox proportional hazards ratio will be used to identify if PD is a risk factor for incident AF after adjusting for significant cofounders. The expected covariates assessed for cofounding and effect measure modification include risk factors for AF and medication.

The Cox proportional hazards ratio will be used to identify association between PD and incident AF after adjusting for relevant confounders previously described in the literature. Several models may be run including covariates --demographic (i.e. age, race, sex), vascular risk factors (i.e. BMI, physical activity, hypertension, smoking, alcohol, socioeconomic status, CAD, CHF and PAD) and medications. These covariates will initially be assessed for evidence of significant confounding of PD→AF, before being included in a final model.

We will assess for effect modification by inflammatory markers in the relation of PD and AF

between periodontal associated inflammation and incident AF, by assessment of stratified analysis as well as introduction of an interaction term.

In order to test the link between PD→AF→cardioembolic stroke, we will also evaluate the relationship between incident AF→stroke subtype. In essence we would be testing if AF is a mediator of the PD→cardioembolic stroke association. Mediation analysis using the Baron and Kenny's causal-steps approach will be used to determine a mediated model. The four steps included will be:

1. The total effect of PD on cardioembolic stroke is significant.
2. The effect of PD on atrial fibrillation is significant.
3. The effect of atrial fibrillation on cardioembolic stroke is significant.
4. The direct effect of PD on cardioembolic stroke adjusted for atrial fibrillation is non-significant.

Exposure Variable	Periodontal disease
Outcome Variable	Incidence of AF
Covariates	Sex Age Race BMI Hypertension Diabetes Smoking Status Alcohol use Socioeconomic Status CAD CHF
Analysis	Cox proportional hazards ratio, Stratified and Mediation Analyses

1. Limitation:

1. Ascertainment of atrial fibrillation: conducted using 3 methods: study ECGs, Hospital discharge codes, and death certificates. It is possible that due to lack of long-term monitoring paroxysmal atrial fibrillation may be missed.
2. Periodontal disease: reliance on single periodontal disease assessment, a limited number of incident stroke subtypes, and owing to the observational nature of our investigation, the possibility of residual confounding cannot be eliminated. Socioeconomic factors such as access to care, income, and health-care behaviors may be potential confounders. However, we adjusted for education levels that in these data serve as a surrogate for the socioeconomic status.

Despite the limitations, this will be the first study to evaluate association between PD and AF. This proposal has important clinical implications and may help us better understand PD-stroke link. For instance: if PD is associated with atrial fibrillation, clinicians should initiate full work up for AF in PD patients, and consider anticoagulation if warranted. Hence the results may help clinicians regarding stroke prevention strategy for PD patients.

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

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)?

Elter JR, Champagne CME, Offenbacher S, Beck JD. 2004. Relationship of periodontal disease and tooth loss to prevalence of coronary heart disease.. J Periodontol. 75(6):782-90.

Beck JD, Eke P, Heiss G, Madianos P, Couper D, Lin D, Moss K, Elter J, Offenbacher S. 2005. Periodontal disease and coronary heart disease: a reappraisal of the exposure.. Circulation. 112(1):19-24.

Alonso A1, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J. 2009;158(1):111-7.

Rifai MAl, Schneider ALC, Alonso A, Maruthur N, Parrinello CM, Astor BC, Hoogeveen RC, Soliman EZ, Chen LY, Ballantyne CM et al.. 2015. sRAGE, inflammation, and risk of atrial fibrillation: results from the Atherosclerosis Risk in Communities (ARIC) Study.. J Diabetes Complications. 29(2):180-5.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X___ Yes ____ No

b. If yes, is the proposal primarily the result of an ancillary study (list number*1996.01)
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.