ARIC Manuscript Proposal #1937

PC Reviewed: 5/8/12  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. **Full Title**: The relationship between periodontal disease and the risk of incident atrial fibrillation: The ARIC study

   b. **Abbreviated Title (Length 26 characters)**: PD and AF Risk: The ARIC study

2. **Writing Group**:

   Writing group members: Olamide Awosanya, James Pankow, Alvaro Alonso, Bryan Michalowicz, James Beck

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

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3. **Timeline**: Data analysis will start upon manuscript approval  
   Manuscript preparation: July 2012  
   Final draft: September 2012
4. **Rationale:**

Periodontal disease is a relatively common disease\(^1\). Several studies have indicated that periodontal infection increases the risk of coronary heart disease (CHD) and cardiovascular disease (CVD)\(^2,3\). Furthermore, periodontitis is associated with levels of systemic inflammatory markers including interleukin-1 (IL-1-beta)\(^4\) IL-6\(^5\), C-reactive protein (CRP)\(^5,6,7\) and tumor necrosis factor alpha (TNF-alpha)\(^8\) all of which have been associated with an increase in the risk CVD\(^9\). In addition, Porphyromonas gingivalis (an organism associated with periodontal disease), has also been associated with an increased risk of cardiovascular disease\(^10\).

Atrial fibrillation is rapidly becoming an epidemic cardiovascular disease\(^11\). Inflammation has been postulated as a predisposing factor for AF, as well as its complications\(^12,13\). The possible association between the generalized inflammatory response caused by periodontal disease and the predisposition to atrial fibrillation (as a result of the inflammatory response), is yet to be investigated in humans, to our knowledge. Animal studies have indicated a possible association\(^14\).

The Dental-ARIC substudy presents to us a valuable resource, with which the relationship between periodontal disease and atrial fibrillation can be investigated in a human population.

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

Our hypothesis is that periodontal disease pathogens trigger specific immune responses, and that these inflammatory responses lead to cardiac injury, which subsequently results in atrial fibrillation. We hypothesize that individuals with periodontitis will have a higher risk of atrial fibrillation independently of other risk factors.

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).**

We will conduct a follow-up analysis of the Dental-ARIC cohort, using visit 4 as baseline.

**Inclusion criteria**
Participation in the Dental ARIC ancillary study,

**Exclusion criteria**
Prevalent atrial fibrillation cases at visit 4, and individuals with missing information on any of the exposure variables of interest.
**Variables of interest**

The exposure is periodontal disease (PD) /periodontitis. At visit 4, a sub study (Dental ARIC) was conducted to assess the role of periodontal disease in the genesis of cardiovascular disease. 6793 participants underwent dental exam for periodontitis during this visit. Periodontitis was rated as:

1) severe periodontitis: ≥ 2 interproximal sites (not on same tooth) with ≥ 6-mm clinical attachment level and ≥ 1 interproximal site with probing depth ≥ 5 mm;
2) moderate periodontitis: >2 interproximal sites with clinical attachment loss > 4 mm (not on same tooth); OR > 2 interproximal sites with probing depth > 5 mm (not on same tooth)
3) mild periodontitis: >2 interproximal sites with > 3mm clinical attachment loss, and > 2 interproximal sites with > 4 mm pocket depth (not on same tooth) or 1 sites with > 5 mm probing depth.
4) no periodontitis: No evidence of mild, moderate or severe periodontitis.

The outcome of interest is incident atrial fibrillation (AF). AF in ARIC is ascertained in three ways: 12-lead ECGs done in study exams; ICD-9 codes from hospitalization discharges (427.31, 427.32); and death certificates including AF as any cause of death (427.3 or I48). Prevalent AF cases at baseline (visit 4) will be defined using information collected at visits 1-4 and previous hospital discharges. Because exam information will not be available beyond visit 4, determination of incident AF will be limited to hospital discharges and cause of death information.

More than 90% of AF cases have been identified from hospital discharges. For this study, we will consider incident AF as any first occurrence of AF between visit 4 and December 31, 2009. There are an estimated >800 incident cases of AF available for analysis in the full cohort occurring after visit 4, but the number available among participants in the Dental-ARIC ancillary study will be lower than this (between 300-400 events).

Covariates (for periodontal disease) measured in Dental-ARIC participants include:
- Systemic markers of inflammation e.g. sICAM, IL-6, and CRP.
- Immunoglobulins associated with common periodontal disease-causing bacterium e.g P.gingivalis.
- Bacterial pathogen burden assessments

Other variables to be considered for analysis as covariates or possible confounders include: age, BMI, height, diabetes, systolic blood pressure, use of antihypertensive medication, smoking status and history (cigarette-years), gender, race, socioeconomic status (level of education), history of heart disease, and alcohol intake.

**Data Analysis**
Primary analyses:

We will estimate association of periodontal disease with incident AF using Cox proportional hazards models. Hazard ratio estimates and 95% confidence intervals will be provided. We intend to run a series of models with additional adjustment for potential confounders, and to highlight effect modifiers.

Secondary analyses:

(1) Multivariate analysis of the association between inflammatory mediators (i.e., CRP) and atrial fibrillation, stratified by periodontal disease status (to examine periodontal disease as an effect modifier). These analyses are motivated by previous analyses in ARIC suggesting effect modification by periodontal disease on risk of other CVD phenotypes.

(2) Multivariate analysis of the direct association between periodontal pathogens and AF.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ___ Yes ___ 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 ICTDER03 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 ___ 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)?
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* 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.


