ARIC Manuscript Proposal #2869

PC Reviewed: 10/11/16 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
Endodontic infection and incident CVD in the ARIC cohort

b. Abbreviated Title (Length 26 characters):
Endodontic infection and CVD

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

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3. Timeline:

Obtain data set: Fall 2016
Complete statistical analysis: Winter 2016/2017
Complete manuscript: Summer 2017

4. Rationale:

Numerous epidemiologic studies have found associations between periodontal disease and prevalent CVD.[1] Several mechanisms linking periodontitis and cardiovascular disease have been proposed including systemic infection, inflammation, and autoimmunity induction.[1] Existing studies have shown that periodontitis is associated with levels of systemic inflammatory markers including interleukin-6 (IL-6)[2], C-reactive protein (CRP)[2, 3], and soluble intercellular adhesion molecule-1 (sICAM-1)[4]. These inflammatory markers have also been associated with increased risk of cardiovascular disease[3, 5, 6]. Endodontic infections and CVD have not been studied as extensively but may be related to cardiovascular disease through these same mechanisms.[7] Endodontic infection is infection of the dental root canal system in the pulp of the tooth and the major etiologic agent of apical periodontitis.[8]

In 2009, Caplan et al used the D-ARIC data to show a cross sectional association between endodontic therapy and CHD.[7] Since then, several other studies evaluating apical periodontitis and CVD have been published with mixed results.[9] Two recent studies using cross sectional[10] and retrospective cohort[11] study designs found associations between apical periodontitis and composite CVD outcomes in small samples. To our knowledge, the associations between endodontic infection and VTE or endodontic infection and heart failure have not previously been considered. Further, the inconsistent findings, small sample sizes, and lack of prospective study designs in previous studies suggest the need for further research to evaluate the impact of endodontic infections on CVD.

We propose to use the longitudinal data from ARIC and the dental ancillary study to examine the relationship between endodontic infection and CVD.

5. Main Hypothesis/Study Questions:

We hypothesize that endodontic infection will be independently associated with CVD risk among ARIC participants.

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 Design:
We will use a prospective cohort study design. Visit 4 (1996-1998) will be used as the baseline for these analyses. Participants will be followed until year-end 2013.

Inclusion/Exclusion:
All ARIC participants who completed the dental history questionnaire at exam 4 will be included (n=11,413). Those with preexisting CHD, Ischemic Stroke, Heart Failure, and VTE will be excluded from the analyses.

Exposure/Outcome:
Data from the ARIC visit 4 will be used. The exposure of interest is self-reported history of root canal therapy. Exposure will be classified according to responses to the questions, "Have you ever had root canal therapy?" and "If (you have had root canal therapy), have you had more than one?" Exposure will be classified as multiple root canals, one root canal, and no root canals according to question responses.

The outcomes of interest are incident CHD, ischemic stroke, heart failure, and VTE. The methods used for ascertainment of outcomes included: (1) participants were contacted annually by phone and interviewed about interim hospitalizations; (2) local hospitals provided lists of hospital discharges with cardiovascular diagnoses, and these were reviewed to identify cohort hospitalizations; and (3) health department death certificate files were continuously surveyed. All discharge codes for cohort hospitalizations and listed causes of death from death certificates were recorded.

Incident CHD was identified as a confirmed CHD death, fatal and nonfatal myocardial infarction, silent myocardial infarction identified by blinded side-by-side electrocardiograph readings read by two technicians independently, coronary artery bypass graph surgery, and/or coronary revascularization.[12]

Incident ischemic stroke was identified and classified as thrombotic or cardioembolic stroke based on discharge codes, signs, symptoms, neuroimaging (computerized tomography/magnetic resonance imaging), and other diagnostic reports.[13]

Incident HF was defined as the first occurrence of either (1) a hospitalization which included an International Classification of Diseases, 9th revision, discharge code of 428 (428.0 to 428.9) in any position, or (2) a death certificate with a 428 (HF) or ICD-10 code I50 (HF) in any position.[14]

Incident VTE was defined as all PEs and DVTs occurring in the legs and was identified using diagnosis codes, hospital records, physician and consultant reports, discharge summaries, and vascular and radiologic imaging, and were validated according to LITE study protocol.[15]

Each outcome will be analyzed separately. Separate manuscripts may be pursued based on the results of the analyses.

Analysis:
Cox-proportional hazards regression models will be used to estimate hazard ratios and 95% confidence intervals between levels of endodontic therapy. Hazards among those who report having had a single root canal therapy, and those having had multiple root canal therapies will be

compared against those without prior root canal therapy (referent). Crude models and those adjusting for potential confounders will be constructed. Known confounders including age, sex, race/center, education, smoking, diabetes, and hypertension will be included. Additional confounders will be evaluated for potential inclusion based on the methodology used by Caplan et al[7] including income, waist to hip ratio, BMI, LDL cholesterol, HDL cholesterol, triglycerides, usual medical care payment mechanism, and having a current dentist.

Those who reported never having had endodontic therapy consist of two highly disparate subgroups: those who had good oral health and never needed a root canal and those who had poor oral health and needed root canals but never had received them. Since number of teeth is a good proxy for access to dental care, we will include an interaction term for number of teeth and reported endodontic therapy in the models similar to the approach used by Caplan et al.[7]

Follow- up time begins at entry into the study (visit 4) and extends to the first outcome, dropping out of the study, death, or else, December 31, 2013.

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 __X__ 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)?

#807 - Relationship between endodontic inflammation and cardiovascular outcomes
This is the proposal that led to the publication by Caplan et al.[7]

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.

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 ____ Yes __X__ No.

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