

ARIC Manuscript Proposal #2676

PC Reviewed: 12/8/15
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title:

Periodontal disease and Incident Venous Thromboembolism: The ARIC Study

b. Abbreviated Title (Length 26 characters):

Periodontitis and VTE: ARIC

2. Writing Group:

Writing group members:

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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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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).

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3. Timeline:

Obtain data set: Fall 2015

Complete statistical analysis: Winter 2015/2016

Complete manuscript: Spring 2016

4. Rationale:

Periodontitis is a chronic inflammatory disease caused by bacterial infection of the supporting tissues around the teeth¹. Periodontitis is common with 46% of US adults having periodontitis and 8.9% having severe periodontitis². Periodontitis is a significant contributor to tooth loss among adults in the United States³. Multiple studies have found an association between periodontal infection and increased risk of coronary heart disease (CHD) and cardiovascular disease (CVD)^{4,5}.

Venous Thromboembolism (VTE), comprising venous thrombosis (VT) and pulmonary embolism (PE), is a common, life-threatening disease in the United States with over 500,000 hospitalized VTE cases annually⁶. The Longitudinal Investigation of Thromboembolism Etiology (LITE) study, including ARIC and CHS found an incidence rate of 1.92 per 1000 person years for VTE in a community-based cohort of middle and older aged individuals⁷. Study participants experiencing a first incident VTE had a 28-day case fatality rate of 11%.⁷.

Existing studies have shown that periodontitis is associated with levels of systemic inflammatory markers including interleukin-6 (IL-6)⁸, C-reactive protein (CRP)^{8,9} and soluble intercellular adhesion molecule-1 (sICAM-1)¹⁰. These inflammatory markers have also been associated with increased risk of cardiovascular disease¹¹⁻¹³ including VTE and may suggest vascular inflammation leading to thrombosis is a possible mechanism by which periodontitis may be associated with VTE¹⁴.

To our knowledge, two previous studies have considered a possible association between periodontitis and venous thromboembolism. Sanchez-Siles et al. used a case-control study design in which 97 patients with VTE and 100 healthy controls were compared for prevalent periodontal disease. They found that periodontitis was more prevalent in VTE patients than controls ($p < .001$)¹⁵. The second study also by Sanchez-Siles et al. used a cross sectional study with 142 patients to evaluate periodontal disease as a risk factor of recurrent VTE according to d-dimer concentration. They found that D-dimer values were higher in those with periodontal disease compared to those without and the difference was statistically significant ($p = 0.010$)¹⁶. The authors hypothesize that these findings may suggest an association between periodontal disease and risk of recurrent VTE.¹⁶

We propose to use the data from the Dental - Atherosclerosis Risk in Communities (D-ARIC) ancillary study to examine the relationship between periodontal disease and VTE. We hypothesized that periodontal disease will be independently associated with risk of incident VTE.

We will conduct supplemental analysis to assess potential effect measure modification of the periodontitis-VTE relationship by thrombophilia SNPs in the F5, F2, ABO, FGG, and F11 genes.

If periodontitis is found to be a VTE risk factor it could provide motivation and encouragement for periodontitis prevention or early treatment. Further, understanding the impact of periodontitis on VTE risk could help individuals and their clinicians take steps to reduce their otherwise elevated VTE risk.

5. Main Hypothesis/Study Questions:

We hypothesized that periodontal disease will be independently associated with increased risk of VTE 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.

Inclusion/Exclusion:

All ARIC participants who reported being edentulous at exam 4 and those who completed the D-ARIC exam will be included and examined separately. Those with preexisting VTE and those taking anti-coagulants at visit 4 will be excluded from the analysis.

Exposure/Outcome:

The exposure of interest is periodontitis and will be determined using 2 periodontal disease classifications. The first is the clinical case definitions proposed by the CDC Working Group on population-based Surveillance Systems for Periodontal Infections¹⁶.

This 3-level definition is as follows:

- (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 ≥ 4 mm clinical attachment level (not on same tooth) or ≥ 2 interproximal sites with probing depth ≥ 5 mm (not on same tooth);
- (3) No/mild periodontitis: individuals not meeting the above definitions.

The second clinical case definition is the biofilm-gingival interface (BGI) definition¹⁷. It incorporates bleeding on probing (BOP) scores in combination with probing depth measures.

This 5-level definition is as follows:

BGI-H: biofilm-gingival interface-healthy (PD ≤ 3 mm, BOP extent scores $<10\%$ at all sites);

BGI-G: BGI-gingivitis (PD ≤ 3 mm, BOP extent scores $>10\%$ at all sites);

- P1: BGI-deep lesion/low bleeding (PD \geq 4mm, BOP extent scores <10% at all sites);
P2: BGI-deep lesion/moderate bleeding (PD \geq 4mm, BOP extent scores 10% to 50% at all sites);
P3: BGI-deep lesion/severe bleeding (PD \geq 4 mm, BOP extent scores \geq 50% at all sites);

The outcome of interest is VTE, validated in LITE, including all PE's and DVT's occurring in the leg (n=755). The hospital admission date abstracted from the patient medical record will be considered the VTE date.

Analysis:

Cox-proportional hazards regression models will be used to estimate VTE hazard ratios and 95% confidence intervals across stratifications of the CDC and BGI classifications. VTE hazard among those who report being edentulous and those with stages of periodontal disease will be compared against those without periodontal disease (referent). Both crude models and those adjusting for potential confounders including age, race, sex, study center, BMI, smoking status, EGFR, diabetes, and education will be constructed.

Additionally, we will assess the presence or absence of effect measure modification by thrombophilia SNPs using five established VTE SNPs (F5 Leiden rs6025, F2 rs1799963, ABO rs8176719 (O vs. non-O groups), FGG rs2066865, and F11 rs2036914). SNP by periodontitis interaction terms will be included in the regression models and assessed for statistical significance. We will adjust for 10 principal components of ancestry to account for population stratification in African Americans.

Follow-up time begins at entry into the study (visit 4) and extends to the first VTE hospitalization, dropping out of the study, death, or else, December 31, 2011.

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 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 ____ 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.csc.unc.edu/ARIC/search.php>

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)?

1479 - CRP and Venous Thromboembolism Incidence

#1937 - The relationship between periodontal disease and the risk of incident atrial fibrillation: The ARIC study

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

11.b. If yes, is the proposal

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.csc.unc.edu/atic/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.csc.unc.edu/atic/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 for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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 No.

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