ARIC Manuscript Proposal # 2886

PC Reviewed: 11/08/2016	**Status: _____**	**Priority:** 2
SC Reviewed: _____	**Status: _____**	**Priority: _____**

1.a. Full Title:

Association of PD levels with incident ischemic stroke as well as the etiological stroke subtypes in the Atherosclerosis Risk In Communities study

b. Abbreviated Title (Length 26 characters):

2. Writing Group:

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

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3. Timeline: 10/31/2016

4. Rationale:

Periodontitis is an infectious disease, which results in destruction of the tissues around the tooth surface and gingiva, loss of connective tissue attachment, erosion of alveolar bone, and tooth loss. The symptoms are bleeding gum (gingivitis), gingival pockets and bone loss (periodontitis) leading to tooth mobility and eventually tooth loss. Periodontitis is common and increases with age. In a US survey, about half of adults have some periodontitis and almost 10% have severe disease. Periodontitis is related to bacterial infection related systemic inflammation, which is implicated in the etiology of atherosclerosis leading to stroke, heart attack and other cardiovascular disease. Epidemiological studies suggest a link between periodontal disease and stroke. The linkage is derived from cross-sectional, case-control and cohort studies. More recent analyses from large-cohort studies suggest that there is a graded association between tooth loss and stroke, cardiovascular death, and all-cause mortality in patients with stable coronary artery disease. If causal, these associations would be of great importance because of the potential that preventing or treating periodontal disease could reduce the risk of major adverse cardiovascular events including stroke.

Periodontal disease (PD) is a risk factor for ischemic stroke. We propose to assess the graded association of PD levels with incident ischemic stroke as well as the etiological stroke subtypes in the Atherosclerosis Risk in Communities (ARIC) study.

5. Main Hypothesis/Study Questions:

Is periodontal disease associated with increased risk of ischemic stroke? If so, is it highly associated with a specific subtype (large artery atherosclerosis, cardioembolism, or small vessel occlusion)?

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).

7. Study design:

Full-mouth periodontal measurements were collected from 6 sites per tooth, in subjects without prior stroke used to differentiate periodontal profile class (PPC). A Latent Class Analysis was used to identify 7 distinct PPCs that included tooth level periodontal measurements. Stroke diagnoses were based on computer derived diagnosis medical record review and imaging confirmation. Classification required evidence of sudden onset of neurological symptoms lasting ≥24 hours. Strokes were further classified according to etiology as thrombotic, lacunar, and cardioembolic subtypes. Multivariable Cox proportional hazards models will be used to study the relationship between periodontal profile class and ischemic stroke, as well as stroke subtypes (cardioembolic, lacunar or thrombotic).

Limitation:

1. Misclassification of ischemic stroke subtype: According to the algorithm, it requires the presence of a possible cardio-embolic source. Presence of a possible cardioembolic source may not necessarily mean cardioembolism as the etiology of the ischemic stroke. Also, artery-to-artery embolic stroke (e.g., dislodged carotid plaque) is classified in ARIC as "atherothrombotic". Lacunar stroke in ARIC is based on some imaging features, regardless of the presence or absence of a "lacunar stroke syndrome". The definition may miss lacunar strokes with negative scans. Also, some lacunar strokes may be cardioembolic in etiology. Even though current classification does not allow for clear distinction between

these subtypes within a stroke etiological type, we don't necessarily expect misclassification to differ on the basis of migraine history.

2. Individual studies have limitations, which include the use of imprecise measures of periodontal disease, inadequate accounting for potential confounders, and low statistical power for vascular events relevant to the stroke/TIA population. Many of these issues were addressed in a prospective cohort study which evaluated the association between the presence of periodontal disease and recurrent vascular events in stroke/TIA patients. [18] One-hundred-six ischemic stroke or TIA patients were recruited at a single center. At enrollment, patients with high periodontal disease (defined as the highest tertile of attachment loss ≥ 5 mm and coinciding with initial and severe periodontitis) tended to be older, male, African-American, and to have lower education level and annual income; but, did not differ significantly by age, or prevalence of traditional risk factors including smoking, hypertension and cholesterol levels. Of these patients, 27 (26%) had recurrent composite vascular events over a median follow-up period of 24 months and 40 (38%) showed high periodontal disease. The associated Kaplan-Meier curve showed that a significantly higher proportion of patients with high periodontal disease experienced composite events of stroke/TIA/MI/death (47% compared to those who did not exhibit periodontal disease 19%; p=0.02). Periodontal disease was independently associated with composite vascular events (hazard ratio 2.8, 95% CI, 1.2-6.5), after adjustment for potential confounders, the association with high periodontal disease remained significant (hazard ratio 2.8, 95% CI, 1.0-8.0).

Despite the limitations, this will be the first study to evaluate association between periodontal disease and ischemic stroke risk, specifically, setiological stroke subtype risk. This proposal has important clinical implications and may help us better assess whether treatment of periodontal disease can reduce the rate of recurrent vascular events in patients with ischemic stroke or TIA.

Inclusion

Participants in the ARIC study who completed a fourth clinic examination (1996 to 1998) were assessed for periodontal disease. All participants at visit 4 will be included.

All stroke diagnoses (first and recurrent) are based on computer derived diagnosis and physician medical record review, with differences adjudicated by a second physician reviewer. Classification required evidence of sudden or rapid onset of neurological symptoms lasting >24 hours or leading to death, in the absence of evidence of a non-stroke cause. Strokes are further classified according to etiologic subtype as thrombotic brain infarction, lacunar infarction, cardioembolic stroke, ICH, or SAH according to criteria adopted from Nation Stroke Association.

Exclusion

Participants with missing periodontal disease information and those who do not meet the criteria as above will be excluded.

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

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)?

Southerland JH, Moss K, Taylor GW, Beck JD, Pankow J, Gangula PR, Offenbacher S. 2012. **Periodontitis and diabetes associations with measures of atherosclerosis and CHD..** Atherosclerosis. 222(1):196-201.PubMed

Ohira T, Shahar E, Iso H, Chambless LE, Rosamond WD, Sharrett RA, Folsom AR. 2011. **Carotid artery wall thickness and risk of stroke subtypes: the atherosclerosis risk in communities study..** Stroke. 42(2):397-403.PubMed

Folsom AR, Ohira T, Yamagishi K, Cushman M. 2009. **Low protein C and incidence of ischemic stroke and coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study..** J Thromb Haemost. 7(11):1774-8.PubMed

Borrell LN, Beck JD, Heiss G. 2006. **Socioeconomic disadvantage and periodontal disease: the Dental Atherosclerosis Risk in Communities study..** Am J Public Health. 96(2):332-9.PubMed

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.PubMed

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.PubMed

Elter JR, Offenbacher S, Toole JF, Beck JD. 2003. **Relationship of periodontal disease and edentulism to stroke/TIA..** J Dent Res. 82(12):998-1001.PubMed

Beck JD, Elter JR, Heiss G, Couper D, Mauriello SM, Offenbacher S. 2001. **Relationship of periodontal disease to carotid artery intima-media wall thickness: the atherosclerosis risk in communities (ARIC) study..** Arterioscler Thromb Vasc Biol. 21(11):1816-22.PubMed

Beck JD, Pankow J, Tyroler HA, Offenbacher S. 1999. **Dental infections and atherosclerosis.**. Am Heart J. 138(5 Pt 2):S528-33.PubMed

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use

any ancillary study data?__Yes _____x_ 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/

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.