ARIC Manuscript Proposal #3666

PC Reviewed: 7/14/20 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: The Longitudinal Association between Periodontal Disease, Heart Failure Biomarkers, and Incident Heart Failure: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Periodontal Disease and heart failure

2. Writing Group: Rebecca Molinsky, Hamdi Adam, Bing Yu, Amil Shah, Pamela L. Lutsey, Faye Norby, Jim Pankow, Chiadi E. Ndumele, Panos Papapanou, Paolo Colombo, Melana Yuzefpolskaya, Jim Beck, Ryan Demmer (authorship order TBD).

Other interested investigators are welcome to join.

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

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3. Timeline: Analyses to begin June 2020, completed July 2020. First draft August 2020, submit September 2020.

4. Rationale:
HF affects >37.7 million individuals globally. In the US, HF prevalence has been projected to increase by 46% between 2012 and 2030[1]. Patient prognosis after their first HF hospital admission is poor, with a <50% survival rate at five years[2]. Despite recent therapeutic advances in treating HF with reduced ejection fraction[40], HF remains a major problem and there are currently no effective therapies available for treating heart failure with preserved ejection fraction. A recent

American Heart Association (AHA) Presidential Advisory emphasizes that the current pipeline for development of novel therapies is flat and innovative solutions are urgently needed to counteract trends towards increasing rates of cardiovascular death[3,4].

The inflammatory activation paradigm is at the cornerstone of current pathophysiological understanding of HF, contributing to the development and progression of the disease. However, the underlying mechanisms of inflammation have not been clearly elucidated. Adverse microbial exposures along the mucosal surfaces of the digestive tract have been hypothesized as a potential source of inflammatory stimuli through translocation of bacteria and bacterial products, such as endotoxin, into the peripheral circulation. However, studies to date in HF have focused solely on the gut microbiota, while the oral bacterial milieu has never been investigated in this context. A robust literature links periodontitis (a pathological condition characterized by destruction of tooth-supporting tissues and subgingival microbial dysbiosis[5-8]) to systemic inflammation including in ARIC (add citation) and, in turn, to a number of adverse cardiovascular outcomes[9-27]. A prior publication has shown that anti-infective periodontal therapy reduces systemic inflammation[28] and favorably modulates gene expression in circulating monocytes[29]. Moreover, a previous meta-analysis of 20 randomized controlled trials found that C-Reactive Protein (CRP) is reduced after anti-infective periodontal therapy[30]; a conclusion also supported by an AHA Scientific Statement[22]. In addition to the aforementioned prior studies we have reported that among more advanced vs. less symptomatic HFrEF patients, oral and gut microbial diversity is altered concurrent with increased levels of circulating endotoxin and inflammation[31-36].

Despite the intersection of periodontitis, HF and inflammation, limited data exist examining the relationship between periodontitis, systemic inflammation and biomarkers of cardiac risk in large population-based settings of patients free of HF. Additionally, there are no data investigating whether periodontitis is differentially associated with HFrEF vs. HF with preserved ejection fraction (HFpEF).

Here we propose to examine, in ARIC, the relationship between periodontitis and the following outcomes cross-sectionally and longitudinally: i) left ventricular ejection fraction (LVEF); ii) N-terminal pro B-type natriuretic peptide (NT-proBNP). Additionally, we will examine the relationship between periodontist and prevalent and incident HF.

5. Main Hypothesis/Study Questions:

We hypothesize that:

1. Periodontal disease, as assessed from clinical periodontal examination and defined using the Periodontal Profile Class (PPC), biofilm-gingival interface (BGI), Center for Disease Control/American Academy of Periodontology definition (CDC/AAP), and 2017 World Workshop on Classification of Periodontal Disease (AAP/EFP) classification systems will be more associated with: i) higher NT-proBNP; ii) lower LVEF (HFrEF); iii) HFpEF and HFrEF categories.

Design and analysis

Study design

Cross-sectional and longitudinal analyses comprising participants included in the Visit 4 dental ancillary study who also have NT-proBNP (visit 4 and visit 5) and LVEF measures (visit 5 only).

Inclusion criteria

African American or white participants with non-missing demographic information, completed dental components at Visit 4, and who have Nt-proBNP and LVEF data. Edentulous participants will be included for comparison.

Primary Exposures

Periodontal Profile Class (PPC): The PPC method has been previously validated and published by ARIC investigators[37]. Briefly, the analytic approach implemented person-level LCA to identify discrete classes of individuals using seven tooth-level clinical parameters. These parameters were: ≥one site with interproximal clinical attachment level (iCAL) ≥3 mm, ≥one site with probing depth (PD) ≥4 mm, extent of bleeding on probing (BOP) (dichotomized at 50% or ≥three sites per tooth), gingival inflammation index (GI = 0 or GI ≥1), plaque index (PI = 0 or Pl ≥1), the presence/absence of full prosthetic crowns for each tooth, and tooth status (present or absent).

BGI classification: As previously described, the classification is based on two clinical parameters, periodontal probing depth (PPD, ≤3 mm or ≥4 mm) and extent of bleeding on probing (BOP, low, <10%; moderate, 10–<50%; and severe, ≥50%). Subjects with PPD ≤ 3 mm at all sites will be defined as periodontal healthy if BOP is <10% or gingivitis if BOP is 10% or more. Subjects with one or more periodontal pockets or PPD ≥4 mm (deep lesion or periodontitis) are divided into low, moderate, or severe bleeding.

Secondary Exposures

CDC/AAP defined periodontitis[38]: i) no or mild periodontitis = neither moderate or severe periodontitis; ii) moderate periodontitis = ≥2 interproximal sites with clinical attachment loss (CAL) ≥4 mm (not on same tooth) OR ≥2 interproximal sites with PPD≥5 mm (not on same tooth); iii) severe periodontitis = ≥2 interproximal sites with clinical attachment loss (CAL) ≥6 mm (not on the same tooth) and ≥1 interproximal site with PPD≥5 mm.

AAP/EFP defined periodontitis: The AAP/EFP classification system focuses on staging the severity of periodontitis as well as rating the progression of the disease been described in great detail[39]. Periodontitis classification is as follows: i.) Stage I (mild disease) = 1-2 mm interdental CAL, radiographic bone loss (RBL) of <15%, no tooth loss, max probing depth of ≤4 mm—mostly horizontal bone loss; ii.) Stage II (moderate disease) = 3-4mm interdental CAL, RBL of 15-33%, no tooth loss, max probing depth of ≤5 mm—mostly horizontal bone loss; iii.) Stage III (severe disease) = RBL extending to middle third of root and beyond, tooth loss of ≤4 teeth, probing depths ≥6 mm, vertical bone loss of ≥3 mm, furcation involvement Class II or III, moderate ridge defects; iv.) Stage IV (very severe disease) = interdental CAL ≥5 mm, extending to middle third of root and beyond, tooth loss of ≥5 teeth, probing depths ≥6 mm, vertical bone loss of ≥3 mm, furcation involvement Class II or III, moderate ridge defects, sustains masticatory dysfunction, secondary occlusal trauma (tooth mobility degree ≥2), severe ridge defects, bite collapse, drifting, flaring, < 20 remaining teeth (10 opposing pairs).

Edentulism will also be considered as several prior publications suggest that edentulism in many populations reflects tooth loss frequently with periodontitis as the indication. Therefore, edentulism often represents long historical exposure to periodontal inflammation.

Covariates & Potential Effect Modifiers

We will consider adjustments for the following variables: age, sex, education, race, center, insurance status, income, cigarette smoking, pack-years of smoking, physical activity, body mass index, systolic blood pressure, blood pressure medication use, diabetes, HDL cholesterol, LDL cholesterol, lipid lowering medications, prevalent CHD, prevalent stroke, and prevalent heart failure (in analyses for NT-proBNP and ejection fraction).

Outcomes

Outcomes of interest will be defined according to the methodology previously utilized in ARIC. We anticipate using the following outcomes:

- Derived from Visit 4 & 5:
    - NT-proBNP (V4, V5 and change between V4 & V5)
    - LVEF (V5)
    - Prevalent HF at visit 4
    - Incident heart failure:
        - Using AHA guidelines create incident HFpEF and HFrEF categories at visit 5: HFrEF <=40%; vs. HF midrange (40% and < 50%)/ HFpEF (>= 50%)
        - Any incident HF after visit 4

Statistical analysis

Participant characteristics will be described according to categories of the PPC exposure variable.

Cross-Sectional Analyses:

Multivariable generalized linear models will be used to regress visit 4 NT-proBNP on visit 4 periodontal disease.

Longitudinal Analyses:

A longitudinal analysis will also be conducted in which the association between visit 4 periodontitis categories and visit 5 NT-proBNP, LVEF will be assessed as primary outcomes. Additional analyses will consider other measures such as LV structure and mass, and diastolic dysfunction at visit 5. Due to possible skewness, log-transformation will be done on the NT-proBNP variable. We will additionally regress changes between NT-proBNP at visit 4 and visit 5 on periodontal disease categories. In addition, sensitivity analyses will be replicated among those with or without heart failure at visit 4.

The association between periodontal disease categories and incident HF (defined as any heart failure occurring after visit 4) will be assessed using multivariable relative risk regression in generalized linear models with a Poisson distribution and a log link. Finally, multinomial logistic regression will be used to analyze the association between periodontitis and a three-level incident HF outcome at visit 5. The three-level HF outcome will be defined as HFrEF, HFpEF and HF with mid-range EF. A similar analysis will be performed for the diastolic dysfunction outcome.

In longitudinal analyses of incident HF, we will explore the potential to determine if change in NT-proBNP explains (mediates) this relationship. Mediation analyses will be conducted using standard approaches to estimating controlled and natural effects using PROC CASUALMED in SAS.

For all longitudinal analysis, if we see differential follow-up by periodontal category, we will also utilize inverse probability of follow-up attendance weights to consider the impact of loss-to-follow-up bias on our results. For all analysis, a series of nested models will be used. Final decisions about modeling will take place during the analysis. Preliminarily, we envision our models to be structured as follows:

- Crude model
- Model 1 will adjust for age, gender, race/center, education, and health insurance
- Model 2 will additionally adjust for cigarette status (never, former current)
- Model 3 will further adjust for BMI
- Model 4 will further adjust for LDL, prevalent heart failure at Visit 4, anti-hypertension medication, previous CHD, previous stroke, diabetes and SBP.
- Model 5 will further adjust for visit 4 NT-proBNP (only in analyses of visit 5 NT-proBNP)

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

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:

___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)?
ARIC Manuscript Proposal #3179
ARIC Manuscript Proposal #3571

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* 2008.06 (NCS) & 1996.01, 2009.29 (Dental))

___ 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.

References

1. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev.* 2017;3(1):7-11.
2. Roger VL. Epidemiology of heart failure. *Circ Res.* 2013;113(6):646-659.
3. McClellan M, Brown N, Califf RM, Warner JJ. Call to Action: Urgent Challenges in Cardiovascular Disease: A Presidential Advisory From the American Heart Association. *Circulation.* 2019;139(9):e44-e54.
4. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation.* 2015;131(4):e29-322.
5. Tang WH, Kitai T, Hazen SL. Gut Microbiota in Cardiovascular Health and Disease. *Circ Res.* 2017;120(7):1183-1196.
6. Tang WHW, Li DY, Hazen SL. Dietary metabolism, the gut microbiome, and heart failure. *Nature reviews Cardiology.* 2018.
7. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. *Nat Rev Immunol.* 2014;15(1):30-44.
8. Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. *Nat Rev Microbiol.* 2012;10(10):717-725.
9. Demmer RT, Breskin A, Rosenbaum M, et al. The Subgingival Microbiome, Systemic Inflammation and Insulin Resistance: The Oral Infections, Glucose Intolerance and Insulin Resistance Study (ORIGINS). *J Clin Periodontol.* 2016.

10. Demmer RT, Squillaro A, Papapanou PN, et al. Periodontal Infection, Systemic Inflammation, and Insulin Resistance: Results from the Continuous National Health and Nutrition Examination Survey (NHANES) 1999-2004. *Diabetes Care.* 2012;35(11):2235-2242.
11. Arora N, Papapanou PN, Rosenbaum M, Jacobs DR, Jr., Desvarieux M, Demmer RT. Periodontal infection, impaired fasting glucose and impaired glucose tolerance: results from the Continuous National Health and Nutrition Examination Survey 2009-2010. *Journal of Clinical Periodontology.* 2014;41(7):643-652.
12. Demmer RT, Jacobs DR, Jr., Singh R, et al. Periodontal Bacteria and Prediabetes Prevalence in ORIGINS: The Oral Infections, Glucose Intolerance, and Insulin Resistance Study. *J Dent Res.* 2015;94(9 Suppl):201S-211S.
13. Zadik Y, Bechor R, Galor S, Levin L. Periodontal disease might be associated even with impaired fasting glucose. *British dental journal.* 2010;208(10):E20.
14. Choi YH, McKeown RE, Mayer-Davis EJ, Liese AD, Song KB, Merchant AT. Association between periodontitis and impaired fasting glucose and diabetes. *Diabetes Care.* 2011;34(2):381-386.
15. Demmer RT, Desvarieux M, Holtfreter B, et al. Periodontal status and A1C change: longitudinal results from the study of health in Pomerania (SHIP). *Diabetes Care.* 2010;33(5):1037-1043.
16. Demmer RT, Jacobs DR, Jr., Desvarieux M. Periodontal disease and incident type 2 diabetes: results from the First National Health and Nutrition Examination Survey and its epidemiologic follow-up study. *Diabetes Care.* 2008;31(7):1373-1379.
17. Ide R, Hoshuyama T, Wilson D, Takahashi K, Higashi T. Periodontal disease and incident diabetes: a seven-year study. *J Dent Res.* 2011;90(1):41-46.
18. Winning L, Patterson CC, Neville CE, Kee F, Linden GJ. Periodontitis and incident type 2 diabetes: a prospective cohort study. *J Clin Periodontol.* 2017;44(3):266-274.
19. Delahaye F, M'Hammedi A, Guerpillon B, et al. Systematic Search for Present and Potential Portals of Entry for Infective Endocarditis. *J Am Coll Cardiol.* 2016;67(2):151-158.
20. DeStefano F, Anda RF, Kahn HS, Williamson DF, Russell CM. Dental disease and risk of coronary heart disease and mortality. *BMJ.* 1993;306(6879):688-691.
21. Joshipura KJ, Rimm EB, Douglass CW, Trichopoulos D, Ascherio A, Willett WC. Poor oral health and coronary heart disease. *J Dent Res.* 1996;75(9):1631-1636.
22. Lockhart PB, Bolger AF, Papapanou PN, et al. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. *Circulation.* 2012;125(20):2520-2544.
23. Ryden L, Buhlin K, Ekstrand E, et al. Periodontitis Increases the Risk of a First Myocardial Infarction: A Report From the PAROKRANK Study. *Circulation.* 2016;133(6):576-583.
24. Dietrich T, Jimenez M, Krall Kaye EA, Vokonas PS, Garcia RI. Age-dependent associations between chronic periodontitis/edentulism and risk of coronary heart disease. *Circulation.* 2008;117(13):1668-1674.
25. Joshipura KJ, Hung H-C, Rimm EB, Willett WC, Ascherio A. Periodontal Disease, Tooth Loss, and Incidence of Ischemic Stroke. *Stroke.* 2003;34(1):47-52.
26. Wu T, Trevisan M, Genco RJ, Dorn JP, Falkner KL, Sempos CT. Periodontal disease and risk of cerebrovascular disease: the first national health and nutrition examination survey and its follow-up study. *Archives of Internal Medicine.* 2000;160(18):2749-2755.
27. Sen S, Giamberardino LD, Moss K, et al. Periodontal Disease, Regular Dental Care Use, and Incident Ischemic Stroke. *Stroke.* 2018;49(2):355-362.
28. Behle JH, Sedaghatfar MH, Demmer RT, et al. Heterogeneity of systemic inflammatory responses to periodontal therapy. *J Clin Periodontol.* 2009;36(4):287-294.
29. Papapanou PN, Sedaghatfar MH, Demmer RT, et al. Periodontal therapy alters gene expression of peripheral blood monocytes. *J Clin Periodontol.* 2007;34(9):736-747.
30. Demmer RT, Trinquart L, Zuk A, et al. The influence of anti-infective periodontal treatment on C-reactive protein: a systematic review and meta-analysis of randomized controlled trials. *PLoS One.* 2013;8(10):e77441.
31. Demmer RT, Nasiri M, Onat D, et al. Relationship Between Oral Microbiota, Inflammation and Congestion Among Advanced Heart Failure Patients. *The Journal of Heart and Lung Transplantation.* 2018;37(4S):S231.
32. Yuzefpolskaya M, Demmer RT, Onat D, et al. Advanced Heart Failure Patients With Left Ventricular Assist Devices and Heart Transplantation Have Altered Oral Microbial Diversity Alongside Endotoxemia, Inflammation and Oxidative Stress. . *The Journal of Heart and Lung Transplantation.* 2018;37(4S):S126.

33. Demmer RT, Trinh PN, Zuver AM, et al. Relationship between Gut Microbiota, Inflammation and Congestion Among Advanced Heart Failure Patients. *Circulation.* 2017;136(No. Supplement 1):A18591.
34. Yuzefpolskaya M, Demmer RT, Trinh PN, et al. Left Ventricular Assist Devices and Heart Transplantation Reduces Gut Dysbiosis, Endotoxemia, Inflammation and Oxidative Stress in Advanced Heart Failure Patients. *Circulation* 2017;136(Supplement 1):A18827.
35. Yuzefpolskaya M, Nasir M, Onat D, et al. Gut Microbiome-Generated Metabolite Trimethylamine-N-Oxide is Reduced After Heart Transplantation and Continuous Flow Left Ventricular Assist Device Therapy in Advanced Heart Failure Patients. *Journal of Heart and Lung Transplantation.* 2018;37(4 (supplement)):S235.
36. Yuzefpolskaya M, Bohn B, Nasiri M, et al. Gut microbiota, endotoxemia, inflammation, and oxidative stress in patients with heart failure, left ventricular assist device, and transplant. *J Heart Lung Transplant.* 2020.
37. Beck JD, Moss KL, Morelli T, Offenbacher S. In search of appropriate measures of periodontal status: The Periodontal Profile Phenotype (P(3)) system. *J Periodontol.* 2018;89(2):166-175.
38. Eke PI, Dye BA, Wei L, et al. Update on Prevalence of Periodontitis in Adults in the United States: NHANES 2009 - 2012. *J Periodontol.* 2015:1-18.
39. Papapanou PN, Sanz M, Buduneli N, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Periodontol.* 2018;89 Suppl 1:S173-S182.
40. Slade, G. D., Ghezzi, E. M., Heiss, G., Beck, J. D., Riche, E., & Offenbacher, S. (2003). Relationship between periodontal disease and C-reactive protein among adults in the atherosclerosis risk in communities study. *ACC Current Journal Review, 12*(5), 29. doi:10.1016/j.accreview.2003.08.039