1.a. **Full Title:** The Association Between Periodontal Disease and Kidney Function Decline in a Population-Based Cohort Study of African Americans

b. **Abbreviated Title (Length 26 characters):** Periodontal and Kidney

2. **Writing Group:**
   Writing group members: Vanessa Grubbs, Eric Vittinghoff, George Taylor, Michael Griswold, Neil Powe, Kirsten Bibbins-Domingo, James Beck, Abhijit Kshirsagar, Adolfo Correa, Herman Taylor

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

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3. **Timeline:** We will start analyses immediately and anticipate a first draft to co-authors by January 2014. An additional 6 weeks will be needed to complete a manuscript suitable for submission to the P&P committee.
4. **Rationale:**
Because chronic kidney disease (CKD) affects an estimated 13% of the general population\(^1\) and consumed roughly 28% of the 2007 Medicare budget, with the greatest expenditures incurred during the month of dialysis initiation,\(^2\) identifying modifiable factors that slow or prevent CKD progression is essential to decreasing this burden. While poorly controlled diabetes and hypertension are well-established CKD risk factors, efforts to reduce them alone have not yet resulted in a decrease in the prevalence of CKD.\(^1\)

Periodontal disease may represent a new focus for slowing or preventing CKD progression; it is independently associated with a 1.5 to 2-fold increased risk of CKD in cross-sectional studies;\(^3\)\(^-\)\(^5\) is common, with moderate or advanced periodontal disease affecting approximately 18% of the general US population;\(^6\) and its treatment has been shown to improve endothelial function.\(^7\) Further, most forms of periodontal disease are readily prevented and treated with good personal oral hygiene and routine non-surgical periodontal therapy, thus presenting a potentially major opportunity to significantly impact the burden of CKD.

Although periodontal disease is a chronic gram negative bacterial infection of the oral cavity, it is proposed that periodontal disease may lead to kidney function impairment via periodontal pathogens accessing systemic circulation through normal oral health procedures like tooth brushing.\(^8\) As a result, these pathogens can bind specific receptors in the kidney, launching an inflammatory cascade that may lead to sustained local tissue inflammation and fibrosis, with deterioration of renal function.\(^9\)

African Americans are disproportionately affected by CKD, with younger average age of CKD onset\(^10\) and 4-fold greater incidence of end stage renal disease (ESRD) compared to their White counterparts.\(^11\) Given that African Americans also have >2-fold prevalence of periodontal disease\(^12\) relative to the general population, periodontal disease may contribute to the observed disparity.

All Jackson site participants of the ancillary dental study to the Atherosclerosis Risk in Communities study (D-ARIC) went on to be enrolled in the JHS. Because JHS includes repeated measures for kidney function, we have a unique opportunity to examine the association of periodontal disease with kidney function decline over time. Through a longitudinal assessment of the association of periodontal disease and CKD, we can gain important knowledge that may improve the burden of CKD, particularly in the disproportionately affected African-American population.

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

**Aim 1:** To examine the association of periodontal disease on kidney function decline at 5 years (as measured by estimated glomerular filtration rate (eGFR) in a population at high risk for rapid CKD progression.
**Hypothesis 1:** Participants with periodontal disease will be more likely to develop clinically significant kidney decline at 5 years than those without periodontal disease.

**Aim 2:** To examine the extent to which the effect of periodontal disease on kidney function decline varies by dental care use.

**Hypothesis 2:** Participants who report less than recommended dental care use will be more likely to develop clinically significant kidney function decline than those who report recommended access to dental care use.

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).**

Clinical predictors: The primary predictor is periodontal status. Uniform criteria for accurately defining periodontal disease have not been established in epidemiologic studies. We will use two methods to define and compare periodontal disease: (1) the Centers for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) definition, which was created by consensus in 2003 to introduce a standard definition for epidemiologic studies, and (2) the periodontal inflamed surface area (PISA), which takes into account bleeding on dental probing as a marker of active inflammation. D-ARIC consisted of a complete oral examination— including probing pocket depth, bleeding on probing, and gingival recession at all 6 sites for all teeth—thus allowing complete confidence in our ability to categorize periodontal disease.

Primary outcomes: Incident eGFR <60 ml/min/m² using repeated eGFR measurements at baseline (D-ARIC) and Jackson Heart Study Exam 1. GFR will be estimated in two different ways for comparison: 1) creatinine-based MDRD and 2) creatinine-based CKD-EPI equation.

Secondary outcome: Development of macroalbuminuria (≥ 300 mg/g) among those without macroalbuminuria at baseline.

Potential confounders: We will adjust for age, gender, income, education, smoking status, diabetes (self-report, fasting glucose ≥ 126 or taking anti-diabetes medications), hypertension (self-report or BP>140/90), renin-angiotensin-aldosterone system blockade (ACE inhibitors, angiotensin receptor blockers, aldosterone inhibitors), periodontal antibody titers, and dental care.

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### Statistical analysis:

1. **Subjects:** All D-ARIC participants who went on to be followed as part of Jackson Heart Study (n=755). The analysis of incident eGFR<60ml/min/1.73m² will include 723 participants with non-missing eGFR>=60ml/min/1.73m² at the baseline for this study.

2. **Models:** We will use multivariate logistic regression to examine the association of periodontal status on incident eGFR<60ml/min/1.73m² at Jackson Heart visit (5 years). We will adjust for potential confounders including age, gender, co-morbid conditions (e.g. diabetes and hypertension), and tobacco use, and assess modification of the effect of periodontal status by socioeconomic status and antibody titers. In addition, for Aim 2, we will assess modification of the association of periodontal status by dental care use. For the secondary outcome, albuminuria, we will also use logistic models to examine the effect of periodontal status on development of macroalbuminuria (≥ 300mg/g). In addition to adjusting for aforementioned confounders, we will adjust for reported use of angiotensin converting enzyme inhibitors, as well as dose, both as time-dependent covariates.

3. **Minimum detectable effects:** Based on preliminary analyses, 48/723 (6.6%) participants had incident eGFR<60ml/min/1.73m², 363 (50%) had no or mild CDC AAP periodontia, 241 (33%) had moderate periodontia, and 119 (16%) had severe periodontia. In comparisons of the severe to the none-mild group, we will have 80% power in 2-sided tests with alpha of 5% to detect adjusted differences of 10.6 percentage points in incidence of the outcome. For Aim 2, we will have 80% power to detect increments of 11 ml/min/1.73m² in the effect of periodontal status on net decline within subgroups with poor access to dental care, as compared to those with good access, if 50% of participants have poor access; this will increase to 13 ml/min if only 20% of participants have poor access.

### 7.a. Will the data be used for non-CVD analysis in this manuscript?  
___X___ 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  __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.cscu.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_ )

_XX_  B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2002.02)

*ancillary studies are listed by number at http://www.cscu.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.

REFERENCES:
