1.a. Full Title: Association of chronic kidney disease with carotid artery plaque characteristics.

b. Abbreviated Title (Length 26 characters): Kidney disease and plaque


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

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3. Timeline: Analysis to begin with currently interpreted carotid MRI scans and be completed by April 2007

4. Rationale: Individuals with kidney failure have a risk of cardiovascular mortality that is 10-30 times that of the general population. While progression to kidney failure is associated with an enormous economic cost and is the most visible consequence of CKD, persons with CKD are much more likely to die of cardiovascular disease than to reach kidney failure. This elevated cardiovascular risk can be partially explained by the increased prevalence and severity of traditional cardiovascular risk factors common among individuals with CKD (e.g., diabetes mellitus, hypertension, left ventricular hypertrophy, heart failure). Much of the increased risk, however, is left unexplained. The potential association of CKD with subclinical atherosclerosis, specifically, is uncertain, as previous studies have not been able to separate these effects from the abnormalities of cardiac structure and function commonly observed in CKD.

Kidney disease is associated with numerous hormonal and metabolic abnormalities, including calcium-phosphorous imbalance, increased parathyroid hormone and resultant abnormal mineralization. We hypothesize that kidney disease will be specifically associated with an increased prevalence of carotid calcification. Several studies suggest
that atherosclerotic lesions observed in patients with CKD also have increased medial thickness than lesions detected in other individuals. Arteriosclerosis, or large-vessel remodeling, is more common in those with CKD than in others, and can lead to decreased arterial compliance, increased pulse pressure and increased systolic blood pressure.

The National Kidney Foundation defines chronic kidney disease based on both kidney function (represented by an estimated glomerular filtration rate, GFR) and kidney damage (represented by urinary albumin excretion). These two components of CKD, however, may have different effects on plaque progression and characteristics. The detailed information on carotid plaque in the ARIC Carotid MRI Study makes this a uniquely suited resource to explore the associations of CKD with arterial plaque characteristics.

5. Main Hypothesis/Study Questions:

Hypothesis 1: Both kidney dysfunction and albuminuria will be associated with lipid core prevalence and volume, carotid wall thickness, stenosis and presence and extent of carotid calcification.

Hypothesis 2: Both kidney dysfunction and albuminuria will be associated with decreased fibrous cap thickness among individuals with a lipid core.

Hypothesis 3: Albuminuria will be associated specifically with T2 signal changes and increased contrast enhancement of the lipid core and arterial wall, indicative of endothelial dysfunction.

These associations will persist after considering the effects of traditional cardiovascular disease risk factors.

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).

All ARIC MRI participants with the relevant data will be included. No exclusions are expected on the basis of participant characteristics.

GFR will be estimated based on serum creatinine, age, race and sex, using the abbreviated equation from the Modification of Diet in Renal Disease (MDRD) Study. The ARIC MRI measurements were compared to the creatinine assay used in the MDRD study at the Cleveland Clinica. Albuminuria will be assessed by the urinary albumin:urinary creatinine ratio (ACR). Analyses will consider both variables as continuous and in categories as defined by the National Kidney Foundation.

All measurements will use the selected internal carotid artery (SICA). Wall thickness will be assessed at specified locations relative to the flow divider (e.g., 1 slice above, 3 slices above) and at the slice with the greatest mean wall thickness. In addition total wall volume will be examined. Core volume will use measurements from all available slices. Fibrous cap thickness will be assessed at the slice with the greatest lipid core area. T2 signal changes and contrast enhancement will be assessed at specified locations, the slice
with the greatest wall thickness and at the slice with the largest lipid core. Lipid core volume will be studied in modeled adjusting for arterial wall area.

Models will be developed to consider estimated GFR alone, ACR alone, and both predictors together. Interaction between the two predictors will be assessed. Analyses will be adjusted for: (A) age, sex, race, and height, (B) established atherosclerosis risk factors in addition, and (C) standard inflammatory measures (CRP). All analyses will use sampling weights to take the design into account.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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.csec.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)? – No related manuscripts found.

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/](http://www.cscc.unc.edu/aric/forms/)

12. **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.**

**Literature Cited**


