ARIC Manuscript Proposal # 1388

PC Reviewed: 07/08/08   Status: A   Priority: 2
SC Reviewed: ____   Status: ____   Priority: ____

1. a. Full Title: Chronic Kidney Disease and Risk of Subclinical Brain Infarction: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): CKD & Silent Brain Infarct

2. Writing Group:
Writing group members:
Josef Coresh MD, PhD; Tom Mosley, PhD; Brad Astor PhD, MPH; Rebecca Gottesman, MD, PhD; A. Richey Sharrett, MD, PhD; Rulan Parekh, MD, MS; Diane Catellier, PhD
Others welcome (plan to invite Laura Coker, Dean Shibata and David Knopman)

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: Analysis and manuscript preparation will be performed over the next six months.

4. Rationale:
Kidney disease is common, with an estimated 26 million Americans having chronic kidney disease (CKD) in 2000\(^1\) and a predicted prevalence in 2030 of more than 2 million patients with end-stage renal disease (ESRD)\(^2\). It is thought that patients with CKD have advanced vascular disease compared to the general population\(^3\), predisposing
them to stroke. Risk factors for stroke such as hypertension, diabetes, and dyslipidemia, are also commonly associated with kidney disease, and there are also a number of potential stroke risk factors unique to the uremic process.

In cross-sectional analyses, there is a strong association between chronic kidney disease and clinical or subclinical stroke. Whether this reflects the accumulation of shared risk factors during middle life is less clear. In addition, the best measure of this risk from kidney disease has also not been extensively studied. In particular, cystatin-based associations in older individuals may be more associated with stroke than creatinine-based associations. Albuminuria, another marker of chronic kidney disease, is also associated with increased stroke risk. The risk of subclinical strokes with albuminuria, across different levels of kidney function, is less clear.

5. Main Hypothesis/Study Questions:

Using data from the ARIC and ARIC-MRI Study, we will look at subclinical brain infarctions across different levels of kidney function. We hypothesize that CKD in middle-aged and older individuals is associated with incident and prevalent subclinical brain infarctions. In addition, albuminuria will be associated with an increased risk of incident and prevalent subclinical brain infarctions across all levels of kidney function. Both associations will be independent of blood pressure and other stroke risk factors.

6. Data (variables, time window, source, inclusions/exclusions):

Data Source and Study population

All participants who had a brain MRI performed after visit 4, free of prevalent clinical stroke or TIA, will be used for this analysis.

Silent brain infarcts (SBIs) will be defined as MRI evidence of an infarct-like lesion (≥3 mm) in participants who reported no history of stroke or TIA. Prevalent SBIs will be defined as evidence of SBIs on MRI from both Visit 3 and after Visit 4. Incident SBIs will be defined as evidence of SBIs from after Visit 4 but not Visit 3.

Chronic kidney disease (CKD) will be defined based on K/DOQI recommendations as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m² or presence of albuminuria at Visit 4. To calculate eGFR, we will use two separate equations:

1) Creatinine-based using the simplified Modification of Diet in Renal Disease (MDRD) Study equation developed at the Cleveland Clinic:
   \[ eGFR = 186.3 \times (\text{serum creatinine [mg/dL]}^{-0.154}) \times (\text{age}^{0.203}) \times (0.742 \text{ if female}) \times (1.21 \text{ if African American}) \]  

2) Cystatin-based using an equation developed from a pooled analysis of three studies and one clinical population:
   \[ eGFR = 177.6 \times \text{Scr}^{-0.65} \times \text{CysC}^{-0.57} \times \text{age}^{-0.20} \times (0.82 \text{ if female}) \times (1.11 \text{ if black}) \]

Creatinine-based eGFR will be calculated from Visits 1, 2, and 4. Cystatin-based eGFR will be calculated from Visit 4. A modified kinetic Jaffe method was used to measure serum creatinine. Serum creatinine concentration was corrected for interlaboratory differences and calibrated to the Cleveland Clinic measurement by subtraction of 0.24 mg/dL at visits 1 and 2, and addition of 0.18 mg/dL at visit 4. eGFR will be analyzed in both categorical and nonlinear models. Urinary albumin:creatinine ratio also will be calculated and analyzed using clinical cutoffs (microalbuminuria 30-300 mg/g, macroalbuminuria 300+ mg/g) and as a continuous nonlinear variable.
Covariates of interest

Covariates will include sociodemographic characteristics (age, race, gender), smoking status, diabetes status, body mass index, CHD prevalence, time-averaged blood pressure, use of blood pressure-lowering medications, and lipid parameters (HDL cholesterol, LDL cholesterol, triglycerides).

Data Analysis

We will determine the association of subclinical brain infarcts from the MRI after Visit 4 with level of kidney disease. Level of kidney disease will be analyzed as 1) stage of CKD, 2) level of Visit 4 creatinine-based versus cystatin-based eGFR, 3) level of Visit 1 and 2 creatinine-based eGFR, and 4) level of albuminuria. SBIs will be defined as incident or prevalent as noted above to determine if current level of kidney function is associated with development of new infarcts in older individuals. Finally, the joint effect of albuminuria and eGFR will also be analyzed.

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 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 ____ 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 list 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)?

N/A

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*)
___ ______ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 1999.01
*ancillary studies are listed by number at 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.
References


