ARIC Manuscript Proposal #2371

PC Reviewed: 5/13/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Chronic kidney and risk of fracture hospitalization: the Atherosclerosis Risk in Communities study

b. Abbreviated Title (Length 26 characters): CKD and fracture

2. Writing Group:
Writing group members: Annie Voskertchian, Natalie Daya, Andrea Schneider, Shoshana Ballew, Josef Coresh, Lawrence Appel, Elizabeth Selvin, Morgan Grams. Others are welcome to join.

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

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3. Timeline: Data analysis to start after approval of this manuscript proposal, abstract available by December 2014, first draft available by June 2015.

4. Rationale:

Persons with end-stage renal disease (ESRD) face increased risk of bone fracture, with older age, female gender, white race, diabetes, low serum albumin, and low BMI associated with higher risk (1-4, 10). Though limited, evidence also suggests an association between chronic kidney disease (CKD) and bone fracture (5, 6, 9). Nickolas and colleagues (15) examined data from the Third National Health and Nutrition Examination Survey (NHANES III), a multistage survey of non-institutionalized US residents conducted between 1988 and 1994, finding that a history of hip fracture was more common among individuals with CKD Stages 3-4 compared with those without CKD (eGFR > 60ml/min) (OR 2.6, 95% CI, 1.1-4.7). Similarly, in a case-cohort study within the Study of Osteoporotic Fractures, women above the age of 65 years with mild (eGFR<45 ml/min) or moderate (eGFR 45-59 ml/min) kidney disease had elevated risk of hip (HR 5.0, 95% CI, 1.4-18.5, and HR 3.7, 95% CI, 1.2-11.2, respectively) but not vertebral fracture in adjusted analyses (6). The mechanism(s) by which CKD associates with fracture susceptibility – and whether this association extends to earlier stages of CKD determined by the presence of albuminuria – is not known.

Several factors may explain why individuals with chronic kidney disease and ESRD have a higher chance of bone fracture. Compromised kidney function results in metabolic and hormonal imbalances. High levels of serum phosphate, increased secretion of parathyroid hormone (PTH), low levels of serum calcium, and reduced production of 1,25-OH vitamin D are common in kidney disease and might adversely affect bone remodeling (7,8). In addition, medications commonly used in kidney disease can increase risk of falls. Glucocorticoids often used in glomerular diseases and thiazolidinediones used in diabetes can increase risk of falls (2, 3, 5, 10, 12). Similarly, the use of antihypertensive medications including diuretics, beta-blockers, calcium channel blockers, and RAS blockers is associated with higher risk of falls and fall-related injuries, with a relative risk of 1.3-1.4 depending on intensity of use (11).

To evaluate the separate associations of eGFR and albuminuria (ACR) with fracture risk, independent of confounding medications and comorbid conditions, we propose to investigate risk factors for fracture hospitalizations among participants in the Atherosclerosis Risk in Communities study.

5. Main Hypothesis/Study Questions:

Aim 1: Evaluate the association of eGFR with incident fracture hospitalization.

Hypothesis 1: Both continuous eGFR and the presence of reduced kidney function (eGFR <60 ml/min/1.73 m^2) will be associated with fracture risk, independent of demographic factors as well as hypertension, diabetes, and glucocorticoid use.

Aim 2: Evaluate the independent association of ACR with incident fracture hospitalization.

Hypothesis 1: Higher ACR will be a strong and independent risk factor for fracture, independent of demographic factors, kidney disease risk factors, and eGFR

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).

Study Design: Prospective cohort analysis beginning at ARIC visit 4

Inclusion/Exclusion Criteria: The study population will consist of all ARIC participants attending visit 4 with measured baseline covariates. Participants of African-American descent from Washington County or Minnesota or self-reported race other than Caucasian or African-American will be excluded.

Outcome variables: Incident fracture hospitalizations will be identified from surveillance data using an ICD-9-CM code algorithm used previously (13).

Exposure variables: eGFR will be calculated using the CKD-Epi 2009 creatinine equation (14). Albuminuria will be calculated as urine albumin-to-creatinine ratio (mg/g). Glucocorticoid use, thiazide diuretic use, and antihypertensive medication use will be determined from participant self-report at visit 4.

Summary of data analysis: Student's t-tests and chi-square tests will be used to examine difference in continuous and categorical variables by CKD stages, respectively. CKD will be staged according to the K/DOQI staging system with CKD Stages 1-2 representing eGFR $\geq$60 ml/min/1.73 m^2 and ACR >30 mg/g, and Stage 3-5 representing eGFR <60 ml/min/1.73 m^2 regardless of albuminuria. Cox proportional hazards models will be used to quantify the association between baseline covariates and fracture hospitalization. In sensitivity analysis, we will compare associations of cystatin C, beta-2-microglobulin, and beta-trace-protein and incident fracture with that of eGFR based on creatinine and incident fracture.

Potential limitations: Anticipated methodologic limitations include the identification of fracture by hospitalization ICD-9-CM code, a method which is likely specific but not sensitive (does not capture fractures treated in the outpatient setting). The gap between study visit 4 and 5 does not allow for the modeling of eGFR and ACR as time-varying covariates, hence kidney function at baseline may not represent kidney function at the time of fracture.

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 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 __x__ 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)?
#1769 Diabetes, Glycemia and Incident Fracture Risk
#2329 Ankle-brachial index and long-term risk of fractures

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* ___
__x__ 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.

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