ARIC Manuscript Proposal # 1058

PC Reviewed: _01/12/05	**Status: __A__**	**Priority: _2__**
SC Reviewed: __01/13/05	**Status: __A__**	**Priority: _2__**

1.a. Full Title: Kidney Function and Risk of Peripheral Arterial Disease: Results from the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): CKD as a risk factor for PAD

2. Writing Group: Keattiyoat Wattanakit, Aaron R. Folsom, Josef Coresh, Elizabeth Selvin, and Alan T. Hirsch (Order to be determined)

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3. Timeline: Analysis will begin following approval; a manuscript is expected to be completed in May 2005.

4. Rationale:

Data from the National Health and Nutrition Examination Survey (NHANES) III estimate that 8 million people (4.5% of the U.S. population) have chronic kidney disease (CKD), defined by estimated glomerular filtration rate (GFR) between 15-59 ml/min/1.73 m^2, and approximately 300,000 people (0.1%) have end-stage renal disease (ESRD), defined by a GFR < 15, or on dialysis.[1] It is now recognized that the natural course of CKD is often complicated by cardiovascular disease (CVD). Patients with CKD of any degree are at increased risk of developing CVD events[2,3] and death,[4,5] independent of established risk factors. For example, data from a recent community-based study with over 1 million adults reported that the risk of CVD events was strongly inversely related to estimated GFR, with adjusted hazard ratios of 1.4, 2.0, 2.8, and 3.4 for GFR levels of

45-59, 30-44, 15-29, and < 15 ml/min/1.73 m^2, respectively.[5] The risk of all-cause mortality also followed a similar pattern, with adjusted hazard ratios of 1.2, 1.8, 3.2, and 5.9 for GFR levels of 45-59, 30-44, 15-29, and < 15 ml/min/1.73 m^2, respectively.[5]

CKD is also highly associated with peripheral arterial disease (PAD) in cross-sectional studies.[6,7] Whether CKD is associated with incident PAD events has not been well characterized. Previous prospective studies examining the association of CKD and CVD events have either not included PAD as an outcome[2,3] or included PAD in a composite CVD outcome.[5,8] To date, only one prospective study has specifically examined this association.[9] Nevertheless, the cohort of this study was derived from postmenopausal women with documented coronary heart disease (CHD). Hence, robust data from the general population are needed. If a positive association is found, this suggests that a screening ABI may be needed in this high-risk population.

5. Main Hypothesis/Study Questions:

The main hypothesis to be tested is that the risk of PAD is inversely related to level of kidney function.

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

Predictor variable: GFR, calculated by using the equation from the Modification of Diet in Renal Disease (MDRD) Study[10]

Outcome variables: Incident PAD events. They were characterized by one of these criteria: 1) ABI < 0.9 in either visit 3 or 4; 2) hospital discharge ICD-9 code of 443.9 (claudication, peripheral arterial disease NOS, peripheral angiopathy NOS, spasm of artery), 84.11 (toe amputation), 84.12 (foot amputation), 84.15 (below knee amputation), 84.17 (above knee amputation), 38.18 (leg endarterectomy), 39.25 (aorto-iliac-femoral bypass), 39.29 (leg bypass surgery); 4) intermittent claudication (based on Rose Questionnaire) from annual surveillance.

Covariates: age, sex, race, ARIC field center, cigarette smoking, diabetes, LDL and HDL cholesterol, fibrinogen, prevalent CHD, physical activity, body mass index, carotid intima-media thickness, and use of cholesterol medications

Inclusions/exclusions:
Inclusions: participants with baseline serum creatinine
Exclusions: participants with prevalent PAD (ABI<0.9 or intermittent claudication) or missing covariates of interest.

Statistical Analysis:

The primary sample of this analysis includes a total of 14,280 participants who had baseline serum creatinine measured and no prior history of PAD or intermittent claudication. Of these, 6,825 participants had normal kidney function (estimated GFR $\geq$ 90 ml/min/1.73m^2), 7079 had mildly decreased kidney function (estimated GFR between 60-89 ml/min/1.73 m^2), and 376 had moderate-to-severely decreased kidney function (estimated GFR between15-59 ml/min/1.73 m^2). 1015 participants developed incident PAD events during 12.3 years of follow-up, with 454, 516, and 47 events in the normal kidney function, mildly decreased kidney function, and moderate-to-severely decreased kidney function groups, respectively.

We will compare CVD risk factors across the three categories of kidney function with differences assessed using analysis of variance, adjusted for age, sex, race, and ARIC field center. Incident PAD events will be analyzed through the year 2001. For those who developed PAD, length of follow-up will be calculated from the baseline examination to the date of first PAD diagnosis. For the ABI group, we will take either visit 3 or visit 4 date (whichever date ABI first became less than 0.9) as the endpoint date. For the hospitalized PAD and intermittent claudication groups, discharge date and the date when intermittent claudication was first reported will be used as the diagnosis date, respectively.

Age, race, sex and ARIC field center adjusted incidence rates per 1000 person-years will be estimated for the three categories using Poisson regression. With normal kidney function as a reference group, proportional hazards regression will be used to calculate relative risks and 95% confidence intervals of PAD events, adjusting for age, sex, race, and ARIC field center and then additionally for the above CVD risk factors. If the relation appears linear, we will also model GFR as a continuous variable. Furthermore, Kaplan-Meier curves will be created to compare the cumulative probability of PAD events for each category.

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.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)?

Risk Factors for Peripheral Arterial Disease Incidence in Persons with Diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Wattanakit K, Folsom AR, Selvin E, Weatherley BD, Pankow JS, Brancati FL, Hirsct AT. Atherosclerosis (in press).

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. primiarly based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

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:

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2. Manjunath G, Tighiouart H, Coresh J, Macleod B, Salem DN, Griffith JL, Levey AS, Sarnak MJ. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. *Kidney Int*. 2003;63:1121-9.
3. Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL, Coresh J, Levey AS, Sarnak MJ. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol*. 2003;41:47-55.
4. Muntner P, He J, Hamm L, Loria C, Whelton PK. Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. *J Am Soc Nephrol*. 2002;13:745-53.
5. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296-305.
6. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation*. 2004;110:738-43.
7. O'Hare AM, Glidden DV, Fox CS, Hsu CY. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the National Health and Nutrition Examination Survey 1999-2000. *Circulation*. 2004;109:320-3.
8. Fried LF, Shlipak MG, Crump C, Bleyer AJ, Gottdiener JS, Kronmal RA, Kuller LH, Newman AB. Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. *J Am Coll Cardiol*. 2003;41:1364-72.
9. O'Hare AM, Vittinghoff E, Hsia J, Shlipak MG. Renal insufficiency and the risk of lower extremity peripheral arterial disease: results from the heart and estrogen/progestin replacement study (HERS). *J Am Soc Nephrol*. 2004;15:1046-51.
10. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461-70.