ARIC Manuscript Proposal # 1077r

PC Reviewed: _07/26/05	**Status: _A__**	**Priority: _2__**
SC Reviewed: _07/28/05	**Status: _A___**	**Priority: __2_**

1.a. Full Title: Uric Acid and Incident Hypertension in a Biracial Cohort: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): **Uric Acid and Hypertension**

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3. Timeline: Data analysis and manuscript preparation: 4 months; manuscript revision and submission: 3 months

4. Rationale:

The association between uric acid and hypertension was observed over a century ago (1), but in the past it has been unclear whether hyperuricemia played a causal role in arterial hypertension or if it was merely a marker of an underlying pathophysiological process. While uric acid levels have been predictive of hypertension in longitudinal studies (2-8), the relationship between uric acid and blood pressure is confounded by numerous factors, including age, diabetes, obesity, alcohol use, sodium intake or volume status, and renal function. These factors have rendered it difficult to establish a causal role for uric acid in the development of hypertension.

Recent findings in animal models have helped establish possible mechanisms whereby uric acid may lead to hypertension. Hyperuricemic rats have been found to have decreased nitric oxide synthesis and upregulated renin production, leading to sodium-independent elevations in blood pressure (9). Hyperuricemia also causes an afferent arteriolopathy (10) and renal tubular injury (9) which may lead to a sodium-dependent hypertension. In cell culture, uric acid stimulates vascular smooth muscle cell proliferation (11) by inflammatory mechanisms (12). These findings have lead to the hypothesis by Johnson et al. that hyperuricemia causes sodium independent blood pressure elevations, followed by uric acid-independent/ sodium-dependent hypertension mediated through hyperuricemia-induced renal damage(13). In support of this theory, Feig and Johnson observed that hyperuricemia was much more common in children with primary hypertension than in those with secondary hypertension or in controls with normal blood pressure (14). Thus, they argue that in a young population with hypertension, hyperuricemia is a cause of primary hypertension rather than an effect of high blood pressure.

Two recent studies have provided further confirmation that uric acid levels independently predict development of hypertension. A study of the Framingham data revealed that uric acid levels predicted subsequent hypertension independent of age, body mass index, diabetes status, renal function, and other covariates (15). A report from the Bogalusa Heart Study found that childhood uric acid independently predicted diastolic blood pressure over an average of 12 years of follow-up (16). The Bogalusa study found that Caucasians had higher baseline uric acid levels than African-Americans. Furthermore, there was evidence of a possible race-gender interaction: the partial correlation (age-adjusted) between uric acid and diastolic blood pressure was stronger in women than in men, and while the strongest correlation was observed in African-American females ($r=.28$, $p=.001$), the correlation was weakest in African-American males ($r=.12$, $p=.23$). Prior to this study the role of race in the relationship between uric acid and blood pressure had not been explored, but the sample size (N=577) may not have been adequate to fully address this question.

The Atherosclerosis Risk in Community (ARIC) study provides a unique opportunity to elucidate racial differences in the relationship between uric acid levels and incident hypertension in a large biracial cohort. These findings could provide new insights into how the pathophysiology of hypertension may differ by race.

5. Main Hypothesis/Study Questions:

Hypothesis: Uric acid independently predicts incident hypertension, but the strength of this association differs between races.

Primary research questions:

- Do uric acid levels independently predict incident hypertension in middle-aged men and women without treated hypertension at baseline?
- Does the strength of the association between baseline uric acid levels and incident hypertension vary across gender and race strata?

Secondary research questions:

- Does the strength of the association between baseline uric acid levels and incident hypertension vary when stratified by age?
- Is the association between uric acid and incident hypertension attenuated when adjusting for other covariates (e.g. Vitamin C intake, protein intake, fasting insulin, etc.)?
- Does uric acid predict change in systolic and diastolic blood pressure at year nine in subjects who are not taking antihypertensive medications?

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

Visit 1
ANTAPS12
ANTZ01 (height, cm)
ANTZ04 (weight, lb)
ANTZ07A (waist, cm)
ANTZ07B (hips, cm)
CHMAPS12
CHMA08 (BUN, mg/dl)
CHMA09 (Creatinine, mg/dl)
CHMA15 (Uric acid, mg/dl)
CHMA16 (Insulin, uu/ml)
LIPAPS12
LIPA01 (Chol)
LIPA02 (Trig)
MSRPS12
MSAM04AA-MSAM04QA
MSRAHF1-MSRAHF17
STRPS12
STROKE01
SBPAPS12
SBPA21 (SBP)
SBPA22 (DBP)
DTIAPS12
DTIA01-DTIA38
NUTPS12
APROT
PROT
VITC
SODI
ALCO
P_PROT
DERPS12
GENDER
RACEGRP1
V1AGEZ1 (Age visit 1)
HYPTMD01 (BP Tx)
HYPTMD04 (HTN Tx)
HYPERT05
MENOPS01
HORMON02 (HRT)
CURSMK01 (Curr smoke)
LDL02
HDL01
GLUCOS01 (Glucose)
BMI01 (BMI)
WSTHPR01 (WHR)
ETHANL03 (EtOH g/wk)
PRVCHD05 (Prevalent CHD)
DIABTS03 (DM composite)

Visit 2
ANTBPS22
ANTY01 (wt)
ANTY04A (waist)
ANTY04B (hip)
CHMBPS22
CHMB07 (glucose)
CHMB08 (creatinine)
CHMB10 (uric acid)
LIPBPS22
LIPB01A (chol)
LIPB02A (trig)
LIPB03A (HDL)
MSRPS22
MSRAHF1-17
MSBM04B-MSBM20B
SBPBPS22
SBPB21
SBPB22
DERPS22
V2AGEY2
V2FU21
ETHANL24
BMI21
WSTHPR21
DIABST23
HYPERT25
HYPTMD21
HYPTMD23
LDL22
MENOPS21
HORMON22

Visit 3
ANTCPS31
ANTX2 (wt)
ANTX3A (waist)
ANTX3B (hip)
LIPCPS31
LIPC5 (LDL)
LIPC1A (Chol)
LIPC2A (TG)
LIPC3A (HDL)
LIPC4A (Glucose)
DTICPS31
DTIC1-38
NUT2PS31
APROT
PROT
VITC
SODI
ALCO

P_PROT
MSRPS31
MSCM04B-20B
MSRAHF1-17
SBPCPS31
SBPC22
SBPC23
DERPS31
V3AGEX1
V3FU31
ETHANL32
BMI32
WSTHPR31
DIABTS34
HYPERT35
HYPTMD31
HYPTMD32
CURSMK31
HORMON31

Visit 4
ANTDPS41
ANTW2 (wt)
ANTW3A (waist)
ANTW3B (hip)
LIPDPS41
LIPD8 (LDL)
LIPD1A (chol)
LIPD2A (trig)
LIPD3A (HDL)
LIPD4A (glucose)
LIPD5A (2hr glucose)
LIPD6A (creatinine)
LIPD7A (insulin)
MSRPS41
MSDM10C-20C
MSDM4C-9C
MSRAHF1-17
SBPDPS41
SBPD19
SBPD20
DERPS41
V4AGE41
V4futime
ETHANL41
BMI41
WSTHPR41
DIABTS42
HYPERT45
HYPTMD41 (BP Tx)
HYPTMD42 (BP Tx)
CURSMK41
MENOPS41
HORMON41

Exclusion criteria: Baseline use of antihypertensive medication, history of stroke, or prevalent CHD.

Analysis plan:

Cox proportional hazards analyses will be used to evaluate incident hypertension (by interval history, antihypertensive use, systolic blood pressure >= 140 mmHg, or diastolic blood pressure >= 90 mmHg) through Exam 4 by quartiles of baseline uric acid levels in univariate and multivariate models (adjusting for age, race, gender, BMI, baseline systolic and diastolic blood pressure, sodium intake, alcohol intake, diabetes, weight change from baseline, and glomerular filtration rate). Hypertension onset will be estimated at the midpoint between the exam at which it was noted and the previous exam. In sensitivity analyses, hypertension onset will be estimated as follows: If hypertension is detected by interval physician diagnosis or antihypertensive medication use, incidence will be estimated at the midpoint between the current and previous exam (17). If hypertension is detected by examination blood pressure measurement, the date of hypertension incidence will be estimated by linear interpolation using blood pressure values at the current and previous visits (18). Formal tests of race and gender interactions will be performed by adding uric acid*gender and uric acid*race terms to the full model, and proportional hazards models will be repeated after stratification by gender and race. Subsequent analyses will evaluate the ability of uric acid quartile to predict 3-year progression of blood pressure by JNC-7 category (normotension, pre-hypertension, and hypertension) using adjusted logistic regression models.

Since there may be significant measurement error and/or intraindividual measurement variability in blood pressure and uric acid, we propose several sensitivity analyses to assess the robustness of our model. First, we will average Exam 1 and Exam 2 values for blood pressure and uric acid for baseline values, using Exam 2 as the baseline exam for other covariates. Alternatively, we repeat the primary analysis after restricting the cohort to those with a blood pressure < 130/80 at Exam 1, thus minimizing the influence of individuals with high blood pressure but spuriously low measurements at baseline. Finally, we will perform a two-stage analysis, using linear mixed-effects models to estimate baseline blood pressure and uric acid values from baseline and follow-

up measures (19). The proportional hazards analysis will then be repeated using these estimates.

To address our secondary questions, the proportional hazards analysis will be repeated after stratifying the data by age (using a cutoff of 55 years). Additional analyses will evaluate the effect of other covariates on the base model (protein intake, fasting insulin, etc.) in an attempt to explore variables which may be proximal or distal in the causal pathway between uric acid and blood pressure. Furthermore, we will evaluate the relationship between baseline uric acid and Exam 4 blood pressure in participants not taking antihypertensive medications at follow-up using linear regression models, adjusting for confounders. All analyses will be two-tailed with an α-level of .05. Analyses will be performed using SAS 9.1 (Cary, NC).

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)?

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)* _____ _____ _____)

*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.

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