ARIC Manuscript Proposal # 1433

PC Reviewed: 10/14/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Serum uric acid and the risk of atrial fibrillation: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Uric acid and AF

2. Writing Group:

Writing group members:
Leonardo Tamariz, Alanna M. Chamberlain, Sunil Agarwal, Elsayed Soliman, Marietta Ambrose, Ronald J. Prineas, Aaron R. Folsom, Alvaro Alonso, others welcome.

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

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3. Timeline:

- Data analysis: 2 months after proposal approval and data release from the coordinating center.
- First draft of the manuscript: 5 months for appraisal by publication committee.

4. Rationale:

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and is an independent predictor of stroke and mortality [1]. There is mounting evidence suggesting that markers of atrial oxidative activity are independently associated with an increased risk of AF [2]. Reactive oxygen species (ROS) like Nicotinamide adenine dinucleotide phosphate –reduced (NADPH) are the end-product of xanthine oxidase activity (XOA) upregulation due to apoptosis and tissue hypoxia.
Serum uric acid (SUA), a product of XOA, is an inexpensive marker and a proxy of the effects of oxidative stress on the heart [3]. No previous population-based studies have assessed the association between SUA and the risk of new onset of AF.
Identifying a marker like SUA is of importance since this could help to identify individuals with higher risk of AF, who could benefit from therapeutic interventions against oxidative stress damage.
Therefore, in the context of the ARIC Study, we hypothesize that patients with elevated serum uric acid are at increased risk for the development of AF and that this risk is independent of confounding risk factors for cardiovascular diseases.

5. Main Hypothesis/Study Questions:

The aim of this proposal is to determine if there is a relationship between serum uric acid and AF, independent of other cardiovascular risk factors. We hypothesize that individuals with higher serum uric acid will have higher risk of developing AF after adjustment for potential confounders.

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).

We will include Caucasians from Minneapolis, Washington and Forsyth Counties, and African-Americans from Jackson and Forsyth County. Only participants with measure of serum uric acid level at baseline will be included. Participants with pre-existing AF at baseline detected through ECG will be excluded (and those without ECG at baseline). Potential confounding variables for the analyses at baseline will include: age, gender, race, study center, diabetes status, systolic and diastolic blood pressure, use of antihypertensive medication, height, weight, body mass index, physical activity, creatinine, smoking history, waist circumference, alcohol intake, cardiopulmonary diseases (CHD, abnormal lipids, heart failure, stroke, ECG-based left ventricular hypertrophy- Cornell method).

AF ascertainment
We will identify AF cases through two main sources:

- Hospital discharges (ICD-9 code 427.31-Atrial fibrillation)
- ECGs performed at visits 1-4

Individuals with evidence of atrial flutter (ICD-9 code 427.32) but without evidence of AF will not be included as incident cases (preliminary analyses suggest this is a small number of total AF/aflutter cases, approx <5%).

Statistical analysis
We will compare baseline characteristics by quartile of uric acid level. The incidence of AF will be reported in age-, sex- and race-standardized rates across quartiles of uric acid level. Follow-up will start the date of first examination and finish when the participant develops AF, dies, abandons the study, or December 31, 2004 is reached (whatever occurs earlier). Finally, we will report the relative hazard of developing AF using Cox proportional hazards models, adjusting for potential confounding factors (see above). Secondary analyses will explore associations by gender and race. To assess the robustness of our analysis we will include a time dependent covariate to assess the change of uric acid over time (if data available as a sub-analysis of the population). PHA assumptions and assumptions of linearity of effect will be examined. Appropriate actions will be taken if either PHA assumption (include time interaction terms or extended Cox models) or linearity (use dummy variables for quartiles of uric acid) assumption is found invalid. Secondary analyses will explore associations by gender and race.

Limitations
The main limitation in this analysis is the underascertainment of AF cases in the cohort. Individuals with AF not requiring hospitalization will be less likely to be identified in our study. If serum uric acid is associated with an increased risk of hospitalization in patients with AF we might find a biased positive association between serum uric acid and AF. Adjustment for other cardiovascular risk factors and presence of cardiovascular disease will attenuate this problem by partially adjusting for an individuals propensity to be hospitalized for AF.

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 ____ 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 Reviewed, no overlap

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)?

MS #1156. Soliman EZ et al. ECG predictors of atrial fibrillation/flutter and its impact on understanding the ethnic distribution of ischemic stroke in the ARIC study.
MS #1351, Alonso A, et al. Incidence of AF in a biracial cohort: the ARIC study.
MS #313 Correlates of uric acid and its association with asymptomatic carotid atherosclerosis
MS # 501 Uric acid and serum antioxidant capacity: a reaction to atherosclerosis?
MS # 525 Serum uric acid and risk of coronary heart disease
MS # 759 Serum uric acid and risk of ischemic stroke
MS # 1077 Serum Uric Acid Predicts Incident Hypertension in a Biethnic Cohort

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* AS #2008.09)
___ 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/

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

1. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. Arch Intern Med 1998;158(3):229-34.
2. Kim YM, Kattach H, Ratnatunga C, Pillai R, Channon KM, Casadei B. Association of atrial nicotinamide adenine dinucleotide phosphate oxidase activity with the development of atrial fibrillation after cardiac surgery. J Am Coll Cardiol 2008;51(1):68-74.

3. Doehner W, von Haehling S, Anker SD. Uric acid as a prognostic marker in acute heart failure--new expectations from an old molecule. Eur J Heart Fail 2007;9(5):437-9.