

## ARIC Manuscript Proposal #759

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**1. a. Full Title:** Serum uric acid and risk of stroke: Atherosclerosis Risk in Communities (ARIC) Study

**b. Abbreviated Title (Length 26 characters):** Serum uric acid and incident stroke

**2. Writing Group (list individual with lead responsibility first):**

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**3. Timeline: Analysis :** December 2000

**First draft:** May 2001

**4. Rationale:** The contribution of serum uric acid as a risk factor for cardiovascular disease (CVD) has been the subject of many studies (1-10). While some studies have found that hyperuricemia is an independent risk factor for coronary heart disease (CHD), others have concluded that the association was confounded by the relationship of uric acid with established risk factors for CHD such as hypertension, obesity, hyperlipidemia, diabetes mellitus, older age, male gender and insulin resistance (11-21). These relations suggest that the observed association between uric acid level and cardiovascular disease may represent an epiphenomenon, reflecting the complex relation between uric acid and other risk factors. At the same time, these inter-relations complicate efforts to establish the independence of uric acid as a cardiovascular risk factor using conventional statistical techniques.

While a recent paper addressing the relationship between serum uric acid and cardiovascular mortality sheds light on this association between uric acid and traditional risk factors (22), data from the Framingham cohort continues to be the most cited evidence of a lack of association between uric acid and CHD (9). In the NHANES I study 5926 subjects who were 25-74 years of age were assessed for ischemic heart disease mortality, total cardiovascular mortality, and all cause mortality, compared by quartiles of serum uric acid level (22). After an average of 16.4 years of follow-up, 1593 deaths occurred with almost half being ascribed to cardiovascular disease. Serum uric acid had a positive relationship to cardiovascular mortality in men and

women and in black and white persons. Further analysis, stratifying by cardiovascular risk status, diuretic use and menopausal status confirmed a significant association of uric acid and cardiovascular mortality in all subgroups except among men using diuretics and men with one or more cardiovascular risk factors. Of interest, even among subjects with low cardiovascular risks (those without increased cholesterol level, hypertension or diabetes), the investigators found that serum uric acid was a predictor of cardiovascular mortality. This association is very unlikely to be confounded by other factors in this low risk subject. In contrast, however, serum uric acid was not correlated with coronary heart disease incidence in the ARIC study after uric acid level was adjusted for other concomitant risk factors (10).

The relationship between uric acid and stroke is even less clear. Lehto et al addressing whether uric acid level is an independent risk factor for stroke, studied over 1,000 patients with non-insulin diabetes, age 45 to 65 years at baseline (23). The average follow-up for this cohort was 7 years. The incidence of stroke increased significantly by quartiles of serum uric acid level. This association remained statistically significant after adjustment for other traditional cardiovascular risk factors. Other studies including that of Bansel et al where serum uric acid level were measured in 50 patients with ischemic thrombotic cerebral vascular disease, hyperuricemia was more frequent in those with abnormal angiograms and uric acid levels were related to abnormalities (24). Moreover, studies performed with carotid ultrasound or angiography suggest that there is a linear relationship between carotid atherosclerosis and hyperuricemia (25). A recent paper from Congo also demonstrated that hyperuricemia, at least among African patients, is a strong predictor of myocardial infarction in men, stroke in both sexes and all cause mortality in women (26). This relationship between uric acid and cardiovascular disease in general and stroke in particular is not limited to the observational studies cited above. Data from approximately 25,000 hypertensive participant who constituted the control groups from 8 controlled clinical trials (including the MRFIT, SHEP, STOP, HDFP, and others) looking at fatal strokes, fatal coronary events, and cardiovascular mortality reveals that uric acid was associated with an increased risk for these three outcomes (27). The magnitude of this risk, surprisingly was similar to that of blood pressure and total cholesterol (27).

All in all, the evidence linking serum uric acid to CHD is somewhat non-uniform. The evidence linking it to stroke, however, seems to favor an association. The number of studies, however, addressing serum uric acid and stroke is much less than those addressing coronary heart disease.

Apart from the association between uric acid and other risk factors, there are several plausible mechanisms where by uric acid may have a direct effect on atherogenesis or on the clinical course of cardiovascular disease. First, there is evidence that increased uric acid levels promote oxidation of low density lipoprotein cholesterol and facilitate lipid peroxidation (28). In addition, increased uric acid levels are associated with increased production of oxygen free radicals and each of these factors is well known to play a role in the progression of atherosclerosis (29). Moreover, it has been suggested that elevated uric acid levels are associated with increased platelet adhesiveness and this affect could potentiate thrombus formation in patients with acute coronary syndromes (30). Also there is the potential for uric acid to be a mediator for the development of other risk factors, particularly systemic hypertension. At least two lines of evidence including the Olivetti Heart Study and the Kaiser Permanente Multiphasic

Health Checkup have demonstrated that serum uric acid levels were a strong independent predictor of new onset hypertension (31-32).

**5. Main Hypothesis/Study Questions:** The specific aims of this proposal are: First, to determine the sex-specific, age, race and field center adjusted incidence of fatal and non-fatal strokes in relation to uric acid levels by quartiles. Second, to identify potential confounders, and compute multivariate-adjusted, sex-specific relative risks of stroke.

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

1. Exclusion: Prevalent stroke.
2. Independent variable: Serum uric acid @ visit 1 and 2 .
3. Dependent variable: fatal and non-fatal stroke incidence through 1997
4. Covariates: age,race,ARIC field center, baseline smoking status and amount, systolic and diastolic blood pressures, use of anti-hypertensives, LDL cholesterol, HDL cholesterol, diabetes, fibrinogen, von Willebrand factor, BMI, waist/hip ratio, baseline serum albumin, and white blood cells count, LVH by ECG.
5. Main analysis: Cox proportional hazard regression model will be used to calculate the multivariable adjusted relative risk of incident stroke in relation to categorical (sex and race specific quartiles) or continuous serum uric acid concentration.

**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 ICTDER01 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 ICTDER01 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

**b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES\_DNA = “No use/storage DNA”?** \_\_\_\_ Yes \_\_\_\_ No

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