ARIC Manuscript Proposal # 1654

PC Reviewed: 5/11/10 Status: A Priority: 2
SC Reviewed: _____ Status: _____ Priority: ____
AMONG

1.a. **Full Title**: Blood pressure, diuretic use and the risk of gout in the Atherosclerosis Risk in the Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Blood pressure and gout

2. **Writing Group**:
Writing group members: Mara McAdams, Janet Maynard, Allan Gelber, Alvaro Alonso, Michael Rosenblum and Josef Coresh.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __MM___ [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, first draft available by September, 2010

4. **Rationale**:

The prevalence of gout is increasing in the United States; in 2005, the estimated prevalence in the US was 3 million cases, which has increased from 2.1 million in 1995.[1] This growing disease burden warrants optimal understanding and quantification of gout risk factors. A recent review[2] noted that epidemiologic studies indicate strong associations between gout and chronic conditions.[3-9]; there was concern over which is the cause and which is the effect. One such risk factor is blood pressure. Understanding the role of blood pressure and hypertension in the development of gout is important because 29.3% of Americans aged older than 17 years have hypertension,[10] and 52% of gout patients have a history of hypertension prior to gout diagnosis.[4]

There is a paucity of data quantifying the association of longitudinal blood pressure and the risk of gout. Previous studies have measured a history of hypertension, but none have utilized repeated measures of longitudinal blood pressure, which may better represent the cumulative association of elevated blood pressure on blood pressure-related diseases. The association of blood pressure may be partly due to the effect of diuretic use. Research is needed estimate the association of cumulative blood pressure, diuretic use and gout.

We strive to fill the knowledge gap in this investigative area using the existing and valuable research infrastructure of a long-term prospective cohort: Atherosclerosis Risk in the Communities Study (ARIC). We will test our hypotheses with the following specific aims:

Primary study questions:

Specific Aim 1: **Estimate the association of longitudinal, cumulative exposure of blood pressure with the development of incident gout.** Cumulative blood pressure was measured over a nine-year period. We will adjust for known gout risk factors and test for an interaction of blood pressure and race.

> **Hypothesis 1:** We hypothesize that the longitudinal cumulative blood pressure exposure is associated with incident gout.

Specific Aim 2: **Estimate the association of diuretic use with incident gout independent of confounding by blood pressure.** We will account for potential time-varying confounding of the blood pressure on the association of diuretic use and gout. We will also estimate the association of gout and the type of diuretic (thiazide, loop, or potassium sparing).

> **Hypothesis 2:** We hypothesize that participants treated with diuretics are at increased gout risk controlling for confounding by indication.

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).

Population: For aim 1, we will restrict our analyses to those participants who self-reported gout at visit 4 and were free of gout before visit 2 (to allow for the calculation of cumulative exposure). For aim 2, we will use only those participants who self-reported gout at visit 4 and did not have gout prior visit 1.

Study design: Both aims will be utilize the longitudinal cohort aspect of this data.

Data analysis:

Aim 1: Longitudinal Blood Pressure ARIC

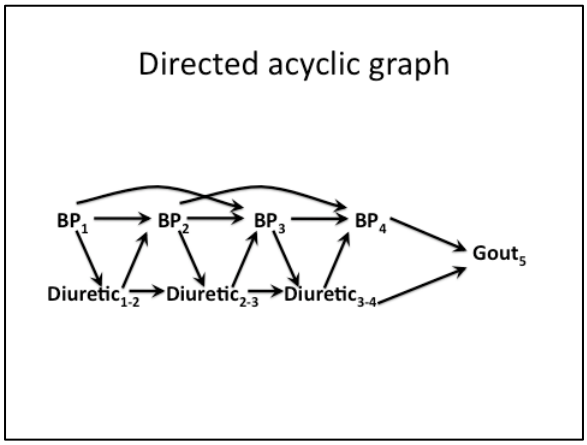
We will estimate the cumulative exposure to blood pressure in ARIC. We will calculate the change in blood pressure between each visit. The area under each change (curve) between each visit will be the cumulative exposure. The cumulative exposure to blood pressure will only be calculated using the blood pressure data that is available prior to the onset of gout. We will not be able to calculate the trajectory for those participants who developed gout between visit 1 and 2, based on the self-reported age of gout onset at visit 4. Therefore, the analysis will be limited to those cases that developed after visit 2. We will conduct a survival analysis to assess the hazard of gout in ARIC, adjusted for age, sex, race, BMI, alcohol intake, kidney function and purine rich food intake. However, we will also adjust for visit 1 and visit 2 serum urate in a second model. As a sensitivity analysis, we will adjust for use of an anti-hypetensive (parameterized as a time-

varying variable). Overall, if we are interested in the association of changes in blood pressure, we would want to account for changes in blood pressure due to anti-hypertnesives.

Aim 2: Longitudinal Blood Pressure and diuretic use ARIC

We will estimate the association of diuretic use on incident gout. We plan to restrict our analyses to patients who did not have gout at the first visit.

Using causal inference models we will account for time-varying anti-hypertensive medication use to estimate the effect of both blood pressure and anti-hypertensive use on the risk of gout in ARIC. In our study, both blood pressure and diuretic use are time-dependent covariates. Blood pressure acts as both confounder and an intermediate of the association between diuretic use and gout. Diuretic use is only initiated with the advent of hypertension and then affects future blood pressure levels (DAG). The standard methods do not account for time-varying confounding of the diuretic-gout association by blood pressure.[11] In this scenario, standard longitudinal methods give biased estimates because the exposure affects a confounder and then future measures are affected by the same confounder. We will account for both systolic and diastolic blood pressure.



We will use marginal structural models to account for time-varying confounding of the association of diuretic use and gout by blood pressure. In this model, we will include inverse probability weights for treatment and censoring. In this analysis, we are assuming that any diuretic that was reported at a given visit was taken prior to the measure of blood pressure. We will use the age of gout onset to determine the timing of gout with respect to the blood pressure and diuretic exposure. The blood pressure and diuretic use that will be included in the marginal structural model will be observed at a visit that is prior to the onset of gout, determined by age. Additionally, we will test whether there is an association between type of diuretic, especially focusing on thiazide diuretics, and dose of the diuretic.

We will compare the results from the marginal structural model to the results from a model that adjusts for time-varying blood pressure and from a model that adjusts for baseline history of hypertension.

- from reading the proposal, I assume that the diagnosis of gout and age of diagnosis were only ascertained at visit 4, right? Maybe you want to clarify it somewhere, as well as include any available information on the validity of the self-reported diagnosis of gout in ARIC.
- I haven't seen a list of the covariates--baseline and time-dependent--you will consider as potential confounders: BMI, education, income, prevalent and incident CVD, diabetes, blood lipids, alcohol, smoking, etc. These are variables potentially associated with your outcome and definitely affecting the probability of receiving diuretics.
- How will you deal with the use of other antihypertensive meds? Related to this, is diuretics vs no diuretics the right comparison? Or is diuretics vs other antihypertensive meds? Using other antihypertensive meds as the

comparison group might help you reduce confounding by indication. Maybe you want to do it as a sensitivity analysis.

Limitations:
Gout was only ascertained at visit 4. Therefore, our sample size is limited to those participants who attended visit 4. Additionally, we only collect diuretic use at the visit and we do not know how long participants have been using the diuretic. Finally, we only have 2 measures of uric acid.

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

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)?

Manuscripts #313, #525, #759, and #1077r plan to study the role uric acid on cardiovascular disease. We plan to focus on similar cardiovascular risk factors on the development of gout.

Additionally, there is a GWAS for longitudinal blood pressure (#1412)

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. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* albuminuria, AS#_2002.02_)

*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.

Works cited:

1. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58:26-35.
2. Saag KG, Choi H. Epidemiology, risk factors, and lifestyle modifications for gout. Arthritis Res Ther 2006;8 Suppl 1:S2.
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4. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. Arch Intern Med 2005;165:742-8.
5. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation 2007;116:894-900.
6. Choi HK, Ford ES, Li C, Curhan G. Prevalence of the metabolic syndrome in patients with gout: the Third National Health and Nutrition Examination Survey. Arthritis Rheum 2007;57:109-15.
7. Fam AG, Stein J, Rubenstein J. Gouty arthritis in nodal osteoarthritis. J Rheumatol 1996;23:684-9.
8. Gelber AC, Klag MJ, Mead LA, et al. Gout and risk for subsequent coronary heart disease. The Meharry-Hopkins Study. Arch Intern Med 1997;157:1436-40.
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10. Ong KL, Cheung BM, Man YB, Lau CP, Lam KS. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. Hypertension 2007;49:69-75.
11. Cole SR, Hernan MA, Robins JM, et al. Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models. Am J Epidemiol 2003;158:687-94.