ARIC Manuscript Proposal # 1733

PC Reviewed: 12/14/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Glycated Hemoglobin and Risk of Incident Hypertension in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): HbA1c and Hypertension

2. Writing Group:
Writing group members: Julie K. Bower, Lawrence J. Appel, Kunihiro Matsushita, J. Hunter Young, Alvaro Alonso, Elizabeth Selvin, others welcome

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

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3. Timeline: We aim to complete this manuscript within 1 year of approval.

4. Rationale:

Glycated hemoglobin (HbA1c), a marker of chronic hyperglycemia, is the standard measure for monitoring glucose control in diabetes patients and is now recommended for use in diagnosis of diabetes {{499 American Diabetes Association 2010; }}. In the ARIC cohort and other studies, elevated values of HbA1c strongly predict the development of diabetes {{491 Inoue,K. 2008; 596 Pradhan, A.D. 2007; 503 Selvin,Elizabeth 2010; }} but are also independently associated with cardiovascular outcomes even in non-diabetic individuals {{597 Adams, R.J. 2009; 595 Blake,G.J. 2004; 601 Sarwar, N. 2010; 503 Selvin,Elizabeth 2010; 594 Selvin,Elizabeth 2004; }}. One pathway by which hyperglycemia may contribute to cardiovascular disease risk is via the development of hypertension.

Approximately 34% of U.S. adults aged twenty years and older have hypertension {{545 Fields,Larry E. 2004; }}, with an additional 25% living with prehypertension {{544 Egan,Brent M. 2010; }}. Hypertension is strongly associated with diabetes and, if left uncontrolled, hypertension will greatly accelerate the development of diabetic complications {{540 Barrett-Conner,Elizabeth 1981; 550 Bell, D.S.H. 2009; 541 Imperatore,Giuseppina 2004; 542 Preis,Sarah Rosner 2009; }}. Further, individuals with diabetes are two to three-times more likely to develop hypertension {{540 Barrett-Conner,Elizabeth 1981; 541 Imperatore,Giuseppina 2004; 542 Preis,Sarah Rosner 2009; }}. Long-term (observational) follow-up of the Diabetes Control and Complications Trial (DCCT) participants with type 1 diabetes demonstrated that intensive glucose control reduced the risk of incident hypertension {{537 de Boer,Ian H. 2008; 606 Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group, 2003; }}. While diabetes and hypertension often co-occur and have shared risk factors, it is plausible that hyperglycemia may be independently associated with increased risk of incident hypertension and that this association is evident in individuals with and without diabetes.

Potential mechanisms through which hyperglycemia might influence blood pressure include endothelial dysfunction {{556 Beevers, G. 2001; 554 Cosentino, F. 2001; 555 Marshall, S.M. 2006; }}, nephropathy {{ 562 Giunti,Sara 2006; 549 Sowers,James R. 2001; }}, and/or increased vascular resistance and stiffness {{556 Beevers, G. 2001; 561 McFarlane,Samy I. 2001; }}. However, the association between hyperglycemia and hypertension risk has not been well characterized, particularly in populations without a history of diabetes. Previous studies have reported an association between single measures of fasting glucose, post-load glucose, and/or fasting insulin with blood pressure and hypertension {{553 Fagot-Campagna,A. 1997; 558 He,Jiang 1999; 557 Liese, A.D. 1999; }}, although some associations have been weak or non-significant {{563 Vaccaro, O. 1996; }}. As HbA1c is a reliable measure of chronic glycemic exposure over the past 2-3 months, examination of the association between HbA1c and incident hypertension in a prospective cohort study will help to better characterize the impact of chronic hyperglycemia on subsequent hypertension risk.

5. Main Hypothesis/Study Questions:

The primary study aim is to quantify the association between HbA1c and incident hypertension. We hypothesize that HbA1c will be positively associated with incident hypertension even after adjustment for known risk factors in persons with and without diabetes.

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).

Study Design. A prospective study design will be used to evaluate the association between measured HbA1c and risk of incident hypertension. HbA1c levels were measured from frozen whole blood samples collected at ARIC Visit 2 (1990-1992) and therefore this visit will serve as the baseline examination for analyses; the reliability of HbA1c measurements from stored samples in ARIC was previously established (26).

Inclusion/Exclusion Criteria. Participants with prevalent hypertension or missing covariates of interest at ARIC Visit 2 will be excluded from the analytic sample. Additionally, individuals with prevalent CHD at Visit 2 will be excluded.

Outcome. Two outcomes will be assessed: 1) visit-based incident hypertension; and 2) self-reported (only) incident hypertension.

Visit-based hypertension (Definition 1): Visit-based incident hypertension will be defined based on the first instance of a measured mean resting blood pressure value of 140 SBP / 90 DBP mmHg or greater at either of the subsequent ARIC visits (Visit 3 or 4), or medication use for blood pressure collected at Visit 3 or 4 (for a maximum 6 years of follow-up).*

Self-reported hypertension (Definition 2): Self-reported incident hypertension will be defined as the first instance of a self-reported diagnosis of hypertension or medication use at either visit 3 or 4 or during the annual telephone calls for over 15 years of follow-up (we will use the most up-to-date AFU files).

*Because clinical practice may have changed over the course of the ARIC cohort study with regards to the use of antihypertensive medications, particularly among those with elevated HbA1c values, a sensitivity analysis will be conducted excluding those cases taking antihypertensive medications.

Covariates of Interest. Adjustment variables (measured at visit 2 unless otherwise noted) will include the following: sex (visit 1), educational attainment (visit 1), income (visit 1), age, clinic site, race, body mass index (BMI), waist circumference, smoking status, alcohol use, Baeke physical activity score, dietary behaviors, lipids, fasting insulin, medications, and estimated glomerular filtration rate (eGFR).

Model 1: Model 1 will include demographic variables (age, sex, race, and clinic site) only.

Model 2: all variables in Model 1 + smoking status, alcohol use, physical activity, BMI, waist circumference, dietary factors (total caloric intake, sodium intake), education, and income.

Model 3: all variables in Model 2 + the following variables, one or more of which may be in the causal pathway from hyperglycemia to hypertension: eGFR, lipids, fasting insulin and diabetes medications (for analyses among those with diabetes).

Potential effect modifiers. We will formally test for effect modification by age, sex, and race/ethnicity.

Data Analysis Summary. Cox proportional hazards models will be used to quantify the association between HbA1c levels and incident hypertension, testing HbA1c both as a continuous and categorical variable. Time of incident hypertension will be defined as the first occurrence of: telephone call where a hypertension diagnosis or blood-pressure lowering medication use was self-reported or the first clinic visit where measured blood pressure values meet the hypertension definition. The primary analyses will be stratified by diabetes status at Visit 2, where diabetes will be defined based on self-reported diagnosis or use of glucose-lowering medication. The primary measures of association that will be reported will be hazard ratios and 95% confidence intervals, adjusted for potential confounding variables listed above.

Among persons without a diagnosis of diabetes at baseline, we will conduct sensitivity analyses censoring cases of incident diabetes that develop during follow-up to assess whether any association between HbA1c and incident hypertension may be mediated by the intervening development of diabetes. While prevalent CHD cases at baseline (Visit 2) will be excluded, additional sensitivity analyses censoring those individuals who develop CHD subsequent to Visit 2 but prior to time at incident hypertension will be conducted. Finally, sensitivity analysis will be conducted excluding individuals with other prevalent conditions associated with hypertension (congestive heart failure, peripheral vascular disease, and history of stroke) or incident cases of these conditions prior to the time at incident hypertension.

Anticipated Methodological Limitations/Challenges. The definition of hypertension will include self-reported data, which may lead to some misclassification of participants regarding hypertension status. To alleviate this concern, we will directly compare results for our analysis of self-reported hypertension status with measured values at the clinic exams. Additionally, our analyses will only include a single measurement of HbA1c and therefore we cannot examine the effect of change in HbA1c levels over time in relation to hypertension risk. Finally, there may be residual confounding due to unmeasured or unknown confounders and bias in the measure of association could be present due to missing potential mediating variables.

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)?

#518, Does Anti-Hypertensive Therapy Predispose to Development of Diabetes Mellitus?

#545, Baseline clinical characteristics and clinical course of cardiovascular disease in individuals with impaired fasting glucose

#1024, Glycemic Control (HbA1c) and Coronary Heart Disease Risk in Persons with and Without Diabetes: The Atherosclerosis Risk in Communities Study

1025, Biological Correlates of Glycemic Control (HbA1c) in Persons with Diabetes

#1596, Hyperglycemia and risk of subsequent elevation of NT-proBNP and hs-cTnT

#1056r, Hemoglobin A1c (HbA1c) and Peripheral Arterial Disease in Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study

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*** 2006.15**)**
___ **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.**