

ARIC Manuscript Proposal # 1334

PC Reviewed: 01/15/08

Status: A

Priority: 2

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title:

Does Orthostatic Hypotension Predict Diabetes: The ARIC Study

b. Abbreviated Title (Length 26 characters):

OH and Diabetes

2. Writing Group:

Writing group members:

Proposed:

Kathryn Rose, Nora Franceschini, Heejung Bang, Marsha Eigenbrodt, Laura Loehr,
Richey Sharrett

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

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3. Timeline:

Preliminary analysis during spring and summer of 2008. Abstract in Fall 2008 and MS by end of 2008.

4. Rationale:

Orthostatic hypotension (OH), is a manifestation of autonomic dysfunction that typically comes to the attention of clinicians when accompanied by symptoms such as dizziness, syncope and falls. Population based studies of OH are mostly limited to the elderly and other high risk populations (1-5). In addition to age, two conditions most consistently associated with OH in clinical reports are hypertension and diabetes, with most reports concluding that these conditions likely preceded OH. In one report based on a middle-aged population, however, OH was predictive of incident hypertension, particularly among those with low normal blood pressure at baseline.(6)

The ARIC Cohort Study offers a unique opportunity for studying OH, as measurements were taken at baseline in an ostensibly healthy population. Among those with OH, most did not report a history of dizziness upon standing – one of the classic presenting symptoms of OH. To date, in the ARIC Study, OH has been associated with incident hypertension (6), coronary heart disease (7), ischemic stroke (8) and increased mortality (9). Further, for CHD and mortality (CVD, all cause), these association persisted in the subset of ARIC participants free of related co-morbidities (e.g., hypertension, CHD, ischemic stroke and diabetes in the case of mortality) (7, 9), suggesting that OH may be a marker of subclinical autonomic dysfunction.

Cardiovascular autonomic dysfunction has been identified as a major contributor to morbidity, reduced quality of life, and mortality among those with diabetes (DM) (10). It has also been identified as one of the pathways whereby diabetes (DM) increases risk for coronary disease (11, 12). Thus, the recognition of subclinical autonomic dysfunction has been identified as important in risk identification and management of persons with diabetes (13, 14). In the ARIC study, reduced heart rate variability – an early measure of cardiovascular autonomic dysfunction (10) – has been associated with DM and related conditions (15, 16, 17). In population-based reports, the cross-sectional association of OH with DM has been inconsistent. In ARIC as well as HDP, in minimally adjusted models, those with DM were approximately twice as likely to have OH as those without DM (3, 7), while in two population-based reports of the elderly these conditions were not related (2, 5).

The purpose of the current study is to assess the association between OH at baseline and a subsequent diagnosis of DM. A secondary purpose will be to examine if OH-DM associations are stronger among those with other indicators of autonomic dysfunction.

5. Main Hypothesis/Study Questions:

OH at baseline will be associated with an increased risk of type II diabetes at subsequent ARIC visits (2-4).

- This association will persist after controlling for sociodemographic characteristics, CVD risk factors.
- This association will be stronger among those with abnormal / unfavorable values on other measures associated with autonomic function (low HRV, high resting heart rate).

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).

This will be a prospective follow-up study.

Our target sample is all participants that had BP change measurements available from the orthostatic BP testing that occurred during the carotid ultrasound exam. Exclusions will include:

- Participants that are not Black or White or Blacks in sites other than MS
- Prevalent DM at baseline
- History of stroke, CHD, heart failure, or cancer at baseline

Our outcome will be incident DM ascertained at visit 2, 3, or 4.

Postural BP measurements were taken with a DINAMAP automated device during the carotid ultrasound exam. Per established guidelines (18), OH will be defined as a decrease in systolic blood pressure of 20 mm Hg or more, or a decrease in diastolic blood pressure of 10 mm Hg or more upon changing from the supine to the standing position.

Covariates / potential effect modifiers evaluated will include: age, sex, race, center, educational attainment, resting SBP and DBP, smoking status and smoking pack years, HDL and LDL cholesterol, IMT, low ABI, BMI, resting heart rate, V1 measures of heart rate variability (based on two minute beat to beat heart rate recordings), use of selected medications (antihypertensive, tricyclic antidepressants, benzodiazepines, phenothiazines), and self-reported health status.

Statistical analysis: The association between postural blood pressure change and incident DM will be modeled using COX proportional hazards regression models. Using the mid-point (or an end-point) of the interval between the last visit without diabetes and the first visit with diabetes as the date of onset of diabetes can lead to invalid inferences (19). Thus, we will use methods developed by Dr. Heejung Bang, a former faculty member in Biostatistics at UNC and ARIC statistician, to estimate/interpolate the date of onset of diabetes with less error. Her algorithm takes into account auxiliary information

(glucose levels before and after onset of diabetes, use of diabetes medications, correction for nonfasting glucose values) to obtain an estimated time/date of onset.

The proportional hazards (PH) assumption will be tested by comparing estimated $\ln(-\ln)$ survival curves of those with and without OH. Crude and age-, gender-, and ethnicity-adjusted PH models will be performed. Other potential effect modifiers and confounders will then be assessed.

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 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
☒ 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.
OK

10. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://www.csc.unc.edu/ARIC/search.php>

☒ 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)?

MS 361-A (OH and Incident CHD, Rose)

MS 1104 (OH and Mortality, Rose)

MS 507 (OH and Ischemic Stroke, Eigenbrodt)

MS ? Approved Fall 2005 (OH and Cognitive Function, Rose)

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ☐ Yes ☒ 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)* _____)**

*ancillary studies are listed by number at <http://www.csc.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.

OK

References

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