ARIC Manuscript Proposal # 1352

PC Reviewed: 03/18/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: __**	**Priority: _**

1.a. Full Title: The association of orthostatic hypotension with incident heart failure

b. Abbreviated Title (Length 26 characters): Orthostasis and HF

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

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3. Timeline: Analysis to begin March 2008, first draft by September 2008.

4. Rationale:

Orthostatic hypotension (OH) is known to be associated with an increased risk of angina and mortality. OH can be co-existing condition in heart failure patients due to HF decompensation or altered fluid status from HF medications. However it is not known whether orthostatic hypotension is a risk factor or pre-existing condition before the development of symptomatic heart failure. One of the normal responses to a postural change is an increase in cardiac output. Heart failure may be due to valvular abnormalites, diastolic dysfunction or systolic dysfunction. Gupta and Lipsitz list diastolic dysfunction or impaired ventricular relaxation as one of the physiologic causes of chronic OH (Gupta, 2007). Furthermore, heart failure patients may have a fixed (HF due to aortic stenosis or hypertrophic obstructive cardiomyopathy) or reduced cardiac output (systolic dysfunction) which would impair response to postural change. In addition, OH has been associated with increased all-cause mortality (Masaki, 1998; Rose, 2006) and an increase in vascular mortality among those with HF (Raiha, 1995).

Existing research on OH has been predominantly in the elderly (Lipsitz, 1989; Enrud, 1992) and other high risk populations (Davis, 1987; Vinik, 2003; Mathias, 1995). To date, in the middle-aged ARIC cohort, OH has been associated with incident hypertension (Rose, 2002), CHD (Rose, 2000), and ischemic stroke (Eigenbrodt, 2000) In the proposed study, we will assess whether orthostatic hypotension is independently associated with incident heart failure. Furthermore, we will determine if the association varies when HF is stratified by whether hypertension and/or CHD is a pre-existing condition with HF. This would be the first population-based cohort to study this association.

5. Main Hypothesis/Study Questions:

Orthostatic hypotension is associated with an increased risk of incident heart failure
-This association persists after adjustment for CVD risk factors and comorbidities.
-We will consider hypertension and CHD as potential modifiers of this relationship.
-This association will persist among the ostensibly healthy subset of baseline ARIC participants (excluding early incident HF cases and those with CHD, stroke, cancer, hypertension, diabetes, and fair or poor perceived health)

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).

Exclusions:

Participants with prevalent heart failure at baseline will be excluded. Criteria to define prevalent HF at baseline are as follows: 1) those answering "yes" to the following question: "Were any of the medications you took during the last two weeks for heart failure?" (N=83), or those with stage 3 or 'manifest HF' by applying Gothenburg criteria (N = 699).

Other exclusions include subjects not black or white, blacks form Minneapolis and Washington County (N = 89), those with missing data for seated blood pressure and those missing or invalid data on postural BP change (N= 2, 376).

Data to be used are as follows:

Variables used to define the main exposure - orthostatic hypotension:

> Supine and standing BP measurements were taken with DINAMAP device during the baseline ultrasound examination. BP change will be calculated as the average of the standing and the supine blood pressure measurements, after the exclusion of the 1st standing measurement. Using established guidelines (see Consensus statement reference) participants will be classified by the presence (a decrease of at least 20 mm Hg SBP or a decrease of at least 10 mm Hg DBP) or absence of OH.

Variables used to define the outcome -incident heart failure through the most recent year available:

> Hospital discharge diagnosis codes ('428.X') and dates for heart failure from cohort eligibility forms (CEL), and death from HF as indicated by codes from death certificates ('428.X or I50) and date of death.
>
> Furthermore, incident heart failure will be stratified based on pre-existing hypertension and then pre-existing CHD. The following variables will be needed: prevalent hypertension at baseline, hypertension status at all 4 visits, prevalent CHD and incident CHD.

Potential confounders and effect modifiers:

> From visit 1 –self-report use of anti-hypertensive medications (specifically, diuretics, and beta-blockers), diabetes, measures of obesity (BMI, WC), hypertension, prevalent CHD, prevalent stroke, smoking, age, education, center, race, and gender, resting heart rate, resting SBP and DBP, IMT, low ABI, LDL, HDL, alcohol use, medication use of tricyclic antidepressants, antiparkinsonians, phenothiazines, and benzothiazines.

Statistical Analysis

This will be a prospective study of the association of postural blood pressure change with incident hospitalized heart failure. Multivariable Cox proportional hazards will be used to model this association. Log negative log survival curves of those with and without OH will be plotted to evaluate the proportional hazards assumption. Age, gender and race will be included in initial models. Then other covariates will be assessed as potential confounders.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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

_____ 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)?

There is overlap in the co-authors in the current proposal with each of the following proposals:

#507 Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. Orthostatic hypotension as a risk factor for stroke: the Atherosclerosis Risk in Communities Study (1987-1996)

#361A Rose KM, Tyroler HA, Nardo CJ, Arnett DK, Light KC, Rosamond W, Sharrett AR, Szklo M. Orthostatic hypotension and incidence of coronary heart disease: the Atherosclerosis Risk in Communities Study

#927 Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (From the Atherosclerosis Risk in Communities [ARIC] study)

#1104 Rose KM, Eigenbrodt ML, Biga RL, Couper DJ, Light KC, Sharrett AR, Heiss G. Orthostatic hypotension predicts mortality in middle-aged adults: the Atherosclerosis Risk in Communities study

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.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

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Rose KM, Eigenbrodt ML, Biga RL, Couper DJ, Light KC, Sharrett AR, Heiss G. (2006) Orthostatic hypotension predicts all cause mortality in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 114:630-6.

Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology*. 1996;46:1470.

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Davis BR, Langford HG, Blaufox MD, Curb JD, Polk BF, Shulman NB. The association of postural changes in systolic blood pressure and mortality in persons with hypertension: the Hypertension Detection and Follow-up Program experience. *Circulation*. 1987;75:340-6.

Mathias CJ. Orthostatic hypotension: causes, mechanisms, and influencing factors. *Neurology*. 1995;45:S6-11.

Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. *Diabetes Care*. 2003;26:1553-79.