ARIC Manuscript Proposal # 3265

PC Reviewed: 11/13/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Isolated Diastolic Hypertension in the Atherosclerosis Risk in Communities (ARIC) Study: Natural History and Implications for Cardiovascular Health

b. Abbreviated Title (Length 26 characters): Isolated Diastolic Hypertension

2. Writing Group:

Writing group members: John W. McEvoy; Natalie Daya; Faisal Rahman; Ron C. Hoogeveen; Roger S. Blumenthal; Amil M Shah; Christie M. Ballantyne; Josef Coresh; Elizabeth Selvin; others welcome

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

First author: **John W McEvoy**
Address: Johns Hopkins School of Medicine,
600 N. Wolfe Street, Blalock 524C,
Baltimore, MD 21287

Phone: 410-955-5857 Fax: 410-367-2151
E-mail: jmcevoy1@jhmi.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: **Elizabeth Selvin**
Address: Johns Hopkins University
2024 E Monument Street, Suite 2-600
Baltimore, MD 21287

Phone: 410-614-3752 Fax: 410-955-0476
E-mail: eselvin@jhu.edu

3. Timeline: We aim to submit this paper for ARIC review <1 year from approval of the manuscript proposal

4. Rationale:

Hypertension can be diagnosed on the basis of an elevated systolic blood pressure (BP), elevated diastolic BP, or elevations in both. Epidemiologic research suggests that risk for cardiovascular disease begins to increase above a systolic BP of 115 mmHg or a diastolic BP of 75 mmHg. Clinical trial data support therapeutic interventions to reduce elevated BP to a systolic target as low as 120 mmHg (SPRINT) and a diastolic target below 90 mmHg (HOT). Based on accumulating data, in particular the Systolic BP Intervention Trial (SPRINT), 2017 clinical practice guidelines published by the American Heart Association (AHA)/American College of Cardiology (ACC) have recently altered the definition to hypertension from a cutoff of 140/90 mmHg to a lower threshold of 130/80 mmHg.[1] To date, European guidelines continue to use the more traditional cutoff for hypertension of 140/90 mmHg. The recommendation in US guidelines to lower the diastolic threshold for hypertension from 90mmHg to 80 mmHg was based on expert opinion and not on trial data, yet this has major implications for an entity known as isolated diastolic hypertension (IDH).

Data from the National Health and Nutrition Examination Study (NHANES) suggest that, based solely on their diastolic BP, many more US adults may be eligible for some form of treatment for their hypertension.[2] However, little is known about the natural history and prognostic implications of IDH (currently defined as a systolic BP < 130 with a diastolic BP ≥ 80 mmHg in the US or a systolic BP < 140 mmHg with a diastolic BP $\geq$ 90 mmHg in the EU or in the past in the US). Indeed, filling this knowledge gap takes on a new urgency given the recent AHA/ACC guideline in effect has changed the definition of this condition. The few prior studies that have been conducted suggest that IDH is more common in younger individuals and may not be associated with CVD outcomes independent of SBP. [3-8]

With rigorous phenotyping and follow-up, as well as access to longitudinal BP measurements and biomarker assessments, data from the Atherosclerosis Risk in Communities (ARIC) Study is ideally positioned to address outstanding questions on the natural history and prognostic implications of IDH. We propose to evaluate the prevalence of IDH in ARIC participants at each of 5 follow-up visits and to characterize the associations between IDH and incident systolic hypertension, IDH and cardiovascular biomarkers (high-sensitivity cardiac Troponin T [hs-cTnT] and NT-proBNP), and IDH and incident cardiovascular disease events.

5. Main Hypothesis/Study Questions:

Aim 1: Isolated Diastolic Hypertension (by both traditional definition and by the 2017 ACC/AHA definition) is more prevalent among younger ARIC participants and the average proportion of IDH, measured during serial follow-up visits, will fall over time in the ARIC study.

Aim 2: Baseline IDH will be associated with incident hypertension based on either systolic BP thresholds, physician diagnosis of hypertension, or drug therapy for hypertension,

Aim 3: Relative to normotension, IDH will be associated cross-sectionally with abnormalities in cardiovascular biomarkers (hs-cTnT and NT-proBNP)

Aim 4: Relative to baseline normotension, IDH will be associated longitudinally with incident cardiovascular disease events (defined as myocardial infarction, fatal coronary heart disease events, or fatal or non-fatal ischemic stroke events), with further evaluation of heart failure and renal outcomes also.

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: Cross-sectional and longitudinal prospective analyses of ARIC data. For the purposes of this analysis, IDH will be defined by the traditional BP cutoff of systolic BP <140 mmHg and diastolic BP ≥90mmHg. However, as a sensitivity analysis, all models will also be reconstructed using an alternative definition of IDH, informed by 2017 US guidelines, of systolic BP <130 mmHg and diastolic BP ≥80mmHg. Data for this study will draw from ARIC visits 1 (1987-1989), 2 (1990-1992), 3 (1993-1995), and 4 (1996-1998).

Hs-cTnT and NT-proBNP: We will analyze biomarker data measured at 2 time points in the ARIC Study using the same high sensitivity (pre-commercial) Roche assay.

> *Visit 2*: cardiac troponin T concentrations were measured from stored (visit 2) serum samples using a sandwich immunoassay method (Roche Diagnostics) implemented on a Roche Elecys 2010 Analyzer in 2012-2013 at the University of Minnesota as part of Dr. Selvin's ancillary study (#2009.16). NT-proBNP was measured in 2012 to 2013 from thawed visit 2 serum samples that had previously been stored at −70°C. Measurements were performed with a sandwich immunoassay method on the Roche Elecsys 2010 Analyzer (Roche Diagnostics Corp, Indianapolis, IN).
>
> *Visit 4*: cardiac troponin T concentrations were measured from stored (visit 4) plasma samples using the same sandwich immunoassay method implemented on a Cobas e411 analyzer in 2010 at the Baylor College of Medicine as part of Dr. Ballantyne's ancillary study (#2008.10). At visit 4, Plasma NTproBNP was measured on a Cobas e411 analyzer using the Elecys proBNP II immunoassay.

Clinical outcomes (Aims 2 and 4): ARIC participants are contacted annually by telephone and reported hospitalizations and deaths are identified by report and active surveillance by surveying lists of discharges from local hospitals and death certificates from state vital statistics offices for potential events. Hospital records are abstracted and potential coronary heart disease and ischemic stroke are adjudicated by an end points committee.

Incident Hypertension: Participants were contacted annually via telephone, with follow-up currently available through 2016. Incident diagnosed hypertension was assessed during these annual telephone calls with the following questions: "Has a doctor ever said you had high blood pressure?" "Since we last contacted you has a doctor said you had high blood pressure?" And "Did you take any medications during the past two weeks for high blood pressure?" In addition, in-visit BP measurement occurred at each ARIC follow-up visit. During these follow-up study visits, BP was recorded as the mean of at least 2 seated measurements with a manual random-zero sphygmomanometer.

Coronary heart disease: We will define incident coronary heart disease cases using the composite definition incorporating definite or probable myocardial infarction, and deaths from coronary heart disease identified during active surveillance for all hospitalizations and deaths among ARIC participants.

Stroke: Abstractors recorded stroke information if the list of discharge diagnoses included a cerebrovascular disease code (International Classification of Diseases, 9th Revision, code 430–437), if a cerebrovascular condition or procedure was mentioned in the discharge summary, or if a cerebrovascular finding was noted on a CT or magnetic resonance imaging report. Eligible cases were classified by computer algorithm and by a physician reviewer, according to criteria adapted from the National Survey of Stroke. Disagreements were adjudicated by another reviewer. Qualifying strokes were further classified into definite or probable hospitalized ischemic stroke (neuroimaging showed acute infarction or no hemorrhage) or hemorrhagic (intraparenchymal or subarachnoid) stroke on the basis of neuroimaging studies or autopsy, when available.

Heart Failure and CKD outcomes captured in ARIC will also be analyzed

Mortality: Death from any cause identified during active surveillance of all participants in the ARIC study.

Sample:

Primary Sample. Of the ARIC participants who attended all or any of the visits 1 through 4, we will exclude participants who were neither white nor black, the small number of black persons in the Minnesota and Washington County cohorts, those missing blood pressure measurements, and those with systolic hypertension (Systolic BP $\geq$ 140 mmHg). In prospective analyses of incident CVD events we will exclude those with a history of MI or ischemic stroke, and those with prevalent CHD or prevalent HF.

Exposure Variables

Categorical exposure: IDH as defined above by both traditional and by new AHA/ACC BP cutoffs. The reference group will be ARIC participants with normotension. Depending on the IDH cutoff being analyzed, normotension will be defined as either BP

<140/90 mmHg (traditional IDH cutoff) or BP <130/80 mmHg (new AHA/ACC IDH cutoff).

Covariates

Models will be adjusted for the following visit 1 variables: age (years), race-center (whites–Washington County, whites-Minneapolis, blacks-Jackson, blacks–Forsyth County, whites–Forsyth County), sex (male or female), smoking (current, former, never), alcohol consumption (current, former, or never), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), body mass index (kg/m^2), eGFR, blood pressure–lowering medication (yes/no), and history of diagnosed diabetes (yes/no).

Aim 1 - Statistical analyses: We will describe the prevalence of IDH at each of the ARIC study visits (1 through 5) included in this analysis.

Aim 2 - Statistical analyses: We will characterize the prospective associations of IDH (assessed at visits 1 through 4) with incident hypertension (defined either by physician diagnosis or by a combination of physician diagnosis, systolic BP >140 mmHg, or antihypertensive drug therapy) recorded a subsequent ARIC visits using Cox models. We will consider the following core models:

Model 1: Crude
Model 2: age, sex, race-center.
Model 3: age, sex, race-center, body mass index (kg/m^2), smoking (current, former, never), alcohol consumption (current, former, or never), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), eGFR, blood pressure–lowering medication (yes/no), and history of diagnosed diabetes (yes/no).
Model 4: all variables in Model 2 + Visit 2 Systolic BP

We will also test for interactions by age, sex, and race.

Aim 3 – Statistical analyses: We will characterize the cross-sectional associations of IDH (assessed at visits 2 and 4) with cardiovascular biomarkers (hs-cTnT and NT-proBNP) measured at the same ARIC visits using logistic models. For these analyses, the biomarker data can be modeled as either continuous or categorical outcomes (for hs-cTnT an elevated level is considered as 14 ng/L and for NT-proBNP an elevated level is considered as 100 pg/mL). We will consider the following core models:

Model 1: Crude
Model 2: age, sex, race-center.

Model 3: age, sex, race-center, body mass index (kg/m^2), smoking (current, former, never), alcohol consumption (current, former, or never), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), eGFR, blood pressure–lowering medication (yes/no), and history of diagnosed diabetes (yes/no).
Model 4: all variables in Model 2 + Visit 2 Systolic BP

We will also test for interactions by age, sex, and race.

Aim 4 – Statistical analyses: We will generate a Kaplan-Meier plot to visually show the survival functions for the different outcomes by categories of IDH versus normotension. We will estimate hazard ratios and their 95% confidence intervals using Cox proportional hazards models with adjustment for covariates. The proportional hazards assumption will be examined using log-(-log) plots and by testing risk factor-by-time interactions; if the assumption is violated the interactions term(s) will be kept in the model and the time-dependent nature of the risk will be interpreted accordingly. We will consider the following core models:

Model 1: Crude
Model 2: age, sex, race-center.
Model 3: age, sex, race-center, body mass index (kg/m^2), smoking (current, former, never), alcohol consumption (current, former, or never), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), eGFR, blood pressure–lowering medication (yes/no), and history of diagnosed diabetes (yes/no).
Model 4: all variables in Model 2 + Visit 2 Systolic BP

We will also test for interactions by age, sex, and race.

We will conduct this analysis in the sample overall, as well as after stratification by hypertension medication treatment status (yes, no, [excluding HTN treatment yes/no in the regression model]).

Sensitivity analyses:

Sensitivity Analysis: All analyses will be repeated for both the traditional and the new AHA/ACC definition of IDH.

Limitations:
- Observational study may be associated with residual confounding
- We may lack power for some of the categories of IDH

REFERENCES

[1]J Am Coll Cardiol. 2018 May 15;71(19):e127-e248.
[2]J Am Coll Cardiol. 2018 Jan 16;71(2):109-118
[3]Franklin S.S., Pio J.R., Wong N.D. Predictors of new-onset diastolic and systolic hypertension – the Framingham heart study. Circulation. 2005;111:1121–1127.
[4]Franklin S.S., Milagros J.J., Wong N.D., L'Italien G.J., Lapuerta P. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES III) Hypertension. 2001;37:869–874.
[5]Fang J., Mafhavan S., Cohen H., Alderman M.H. Isolated diastolic hypertension: a favourable finding among young and middle-aged hypertensive subjects. Hypertension. 1995;26:377–382.
[6]Pickering T.G. Isolated diastolic hypertension. J Clin Hypertens. 2003;5:411–413.
[7]Nielsen W.B., Lindenstrom E., Vestbo J., Jensen G.B. Is diastolic hypertension an independent risk factor for stroke in the presence of normal systolic blood pressure in the middle-aged and elderly? Am J Hypertens. 1997;10:634–639.
[8]Strandberg T.E., Saloman V.V., Vanhanen H.T., Pitkala K., Miettinen T.A. Isolated diastolic hypertension, pulse pressure, and mean arterial pressure as predictors of mortality during a follow-up of up to 32 years. J Hypertens. 2002;20:399–404.

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 ICTDER 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)?

None

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* __2009.16 and 2008.10_____)

___ 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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.