ARIC Manuscript Proposal #2197r

PC Reviewed: 9/10/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Resistant Hypertension in the Atherosclerosis Risk in Communities (ARIC) study: Incidence and Prognosis

b. Abbreviated Title (Length 26 characters): Resistant HTN

2. Writing Group:
Writing group members: Orly Vardeny, Pardeep Jhund, Deepak Gupta, Brian Claggett, Joseph Coresh, Kunihiro Matsushita, OTHERS WELCOME, Scott Solomon

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

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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).

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3. Timeline: Analysis to begin immediately, First draft by January 2014

4. Rationale:

Resistant hypertension is defined as blood pressure that remains above goal despite use of antihypertensive medications from 3 or more drug classes, or the use of 4 or more drug classes to treat hypertension regardless of blood pressure control.[1] Use of a diuretic is recommended as one of the drug classes, and ideally antihypertensive medications are optimally dosed. The prevalence of resistant hypertension is unknown, but is estimated to occur in approximately 15-30% of patients treated for hypertension.[2-6]

Individuals with resistant hypertension are thought to be at increased risk for cardiovascular disease, although studies examining associations between resistant hypertension and cardiovascular outcomes are sparse. Multiple cross sectional analyses reported more frequent co-morbid coronary heart disease, heart failure, stroke, and diabetes among persons with resistant hypertension compared to those with controlled hypertension treated with 1-3 medication classes.[2,3,7] In an analysis of patient data from Kaiser Permanente Colorado and Northern California health care systems, those with resistant hypertension had a 50% increased risk in cardiovascular events after 5 years compared to patients whose blood pressure was controlled on 3 medications.[8] There are limited data regarding longitudinal effects of resistant hypertension on clinical outcomes.

We propose to investigate the relationship between resistant hypertension and the incidence of all-cause mortality, cardiovascular outcomes, and kidney disease, to explore interactions with race/ethnicity, and examine whether duration of resistant hypertension affects clinical outcomes. In contrast to previous studies that have investigated resistant hypertension, the ARIC cohort is a large bi-ethnic sample and offers the potential to explore these relationships in the setting of lengthy follow up.

5. Main Hypothesis/Study Questions:

We hypothesize that resistant hypertension will be associated with an increased risk for mortality, cardiovascular events, and chronic kidney disease. We further hypothesize that individuals with resistant hypertension will exhibit a higher risk for unfavorable clinical outcomes compared to patients with non-resistant hypertension and those without a diagnosis of hypertension.

Specific Aims:

4. **To assess the relationship between resistant hypertension at Visits 2 through 4 and subsequent mortality, adverse cardiovascular events, and renal disease. We hypothesize that resistant hypertension will be associated with worse clinical outcomes.**
5. **To assess whether race modifies the relationship between resistant hypertension and cardiovascular events and renal disease. We hypothesize that the relationship between resistant hypertension and cardiovascular events is attenuated in those of Caucasian race.**
6. **To assess whether the duration of resistant hypertension influences the association with adverse clinical outcomes.**

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).
Subjects with prevalent hypertension, heart failure, history of myocardial infarction, Coronary Heart Disease, stroke, and chronic kidney disease (eGFR < 60) at visit one will be excluded. Prevalent heart failure will be defined as either participant reported medication use for heart failure or Gothenberg score=3.

Analysis methods:

Primary Exposure Variable:

- Hypertension status will be defined at visits 2-4 by classifying each subject into one of four categories:
- Resistant hypertension:
    - Blood pressure ≥ 140/90 mmHg with use of ≥ 3 antihypertensive drug classes; or
    - Use of ≥ 4 antihypertensive drug classes regardless of blood pressure
- Hypertension, controlled:
    - Blood pressure < 140/90 mmHg with use of 1-3 antihypertensive drug classes
- Hypertension, uncontrolled:
    - Blood pressure ≥ 140/90 mmHg with use of < 3 antihypertensive drug classes
- Non-hypertension:
    - Blood pressure < 140/90 mmHg without use of antihypertensive drugs

Primary Endpoint: Combined incident myocardial infarction, heart failure, (defined as heart failure hospitalizations or heart failure-related death), stroke, kidney disease (defined as eGFR < 60, need for hemodialysis or renal transplant), all-cause mortality.

Analysis:

5.7. Baseline characteristics will be compared between individuals across hypertension categories using parametric or non-parametric trend tests.

6.8. Hypertension status at visits 2-4 will be related to incident cardiovascular events (myocardial infarction, heart failure, stroke), renal outcomes (eGFR < 60, need for dialysis, kidney transplant) and mortality with Cox regression analysis in univariate and multivariable models adjusting for known confounders as well as those that are apparent based on baseline characteristics. These will include (but not be limited to): age, gender, race, BMI, smoking, diabetes, and elevated serum cholesterol at visit one. We will also test for interactions with race.

7.9. In order to assess the impact of duration of resistant hypertension, resistant subjects at visit 4 will be further classified according to the visit at which they were first observed to have resistant hypertension. Duration of resistant hypertension will then be related to subsequent incident cardiovascular events, chronic kidney disease, and mortality with Cox regression analysis as described in #2.

~~8.~~10. A multinomial logistic regression model will be constructed using patients with resistant hypertension at visit 3 in order to identify characteristics of that are associated with a change from resistant to non-resistant hypertension by visit 4.

Limitations

- Presence of pseudoresistant hypertension (nonadherence, inaccurate measurements, white coat hypertension) cannot be assessed
- Dosing of antihypertensive medications and patient salt intake are not available
- Unknown confounders may exist that are not accounted for in analysis models
- Death from HF assessed by death certificate, which may not accurately capture all HF-related deaths

References

1. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B, Carey RM. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation. Jun 24 2008;117(25):e510-526.
2. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension. Jun 2011;57(6):1076-1080.
3. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. Circulation. Aug 30 2011;124(9):1046-1058.
4. Hanselin MR, Saseen JJ, Allen RR, Marrs JC, Nair KV. Description of antihypertensive use in patients with resistant hypertension prescribed four or more agents. Hypertension. Dec 2011;58(6):1008-1013.
5. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. Mar 23 2002;359(9311):995-1003.
6. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, Mancia G, Cangiano JL, Garcia-Barreto D, Keltai M, Erdine S, Bristol HA, Kolb HR, Bakris GL, Cohen JD, Parmley WW. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA. Dec 3 2003;290(21):2805-2816.
7. de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, Oliveras A, Ruilope LM. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension. May 2011;57(5):898-902.
8. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, O'Connor PJ, Selby JV, Ho PM. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation. Apr 3 2012;125(13):1635-1642.

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**

10. 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)?

There is no overlap with current manuscript proposals. A few relevant publications include the following:

Avery CL, Loehr LR, Baggett C, Chang PP, Kucharska-Newton AM, Matsushita K, Rosamond WD, Heiss G. The population burden of heart failure attributable to modifiable risk factors: the ARIC (Atherosclerosis Risk in Communities) study. J Am Coll Cardiol. 2012 ;60(17):1640-6

Jones CD, Loehr L, Franceschini N, Rosamond WD, Chang PP, Shahar E, Couper DJ, Rose KM. Orthostatic hypotension as a risk factor for incident heart failure: the atherosclerosis risk in communities study. Hypertension. 2012 ;59(5):913-8.

Gottesman RF, Coresh J, Catellier DJ, Sharrett RA, Rose KM, Coker LH, Shibata DK, Knopman DS, Jack CR, Mosley TH. Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis Risk in Communities (ARIC) study. Stroke. 2010 ;41(1):3-8

Rose KM, Eigenbrodt ML, Biga RL, Couper DJ, Light KC, Sharrett RA, Heiss G. Orthostatic hypotension predicts mortality in middle-aged adults: the Atherosclerosis Risk In Communities (ARIC) Study. Circulation. 2006 ;114(7):630-6

Fox E, Taylor H, Andrew M, Han H, Mohamed E, Garrison R, Skelton T. Body mass index and blood pressure influences on left ventricular mass and geometry in African Americans: The Atherosclerotic Risk In Communities (ARIC) Study. Hypertension. 2004;44(1):55-60

Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G. Hypertension, blood pressure, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) study. Hypertension. 2003 ;42(6):1106-11

Arnett DK, Rautaharju P, Crow R, Folsom AR, Ekelund LG, Hutchinson R, Tyroler HA, Heiss G. Black-white differences in electrocardiographic left ventricular mass and its association with blood pressure (the ARIC study). Atherosclerosis Risk in Communities. Am J Cardiol. 1994 ;74(3):247-52

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)* _____ _____ _____)

*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.