ARIC Manuscript Proposal # 2823

PC Reviewed: 8/9/16  Status: _____  Priority: 2
SC Reviewed: __________  Status: _____  Priority: ____

1.a. Full Title: Stroke, CHD and CVD risk by blood pressure, BMI and anti-hypertensive categories

b. Abbreviated Title (Length 26 characters): Obesity and hypertension

2. Writing Group: June Stevens, (in alpha order: Jianwen Cai, Zhaohui Cui, Sydney Thai, Anthony Viera), Eric Whitsel

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

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3. Timeline: Submission to journal 1 year after approval of proposal
4. Rationale:

It is well established that body mass index (BMI) is positively associated with risk of incident hypertension (Chandra et al., 2014; Shihab et al., 2012; Stevens et al., 2008) and that hypertension is a major risk factor for CVD (MacMahon et al., 1990; JNC8, James et al., 2014). Nevertheless, numerous studies have shown that the impact of elevated BMI on stroke and CHD risk is weak or null after adjustments for risk factors such as age, sex, ethnicity, diabetes and blood pressure (Yatsuya et al., 2010; Folsom et al., 1999; Chambless LE et al., 1996; Wormser). This lack of association with BMI could be interpreted to mean that control of body weight is not important for CVD prevention as long as the BMI-sensitive cardiometabolic risk factors are controlled.

The prevalence of obesity has reached historic levels in the United States and Americans find diet and activity changes for obesity prevention and treatment very difficult. Some may reason that if excess weight leads to high blood pressure, concern about elevated CVD risk is small because medications are available to normalize blood pressure. Antihypertensive medications are credited with reducing the risk of CVD since their introduction in the 1940’s (Collins et al., 1990; Freis, 1995), and it is standard care for medications to be recommended when blood pressure is elevated (JNC8, James et al., 2014).

Most studies of hypertension define “hypertensive” participants as those with SBP/DBP ≥140/90 mmHg or using anti-hypertensive medications. Note that participants are defined as hypertensive if they are taking anti-hypertensive medications, regardless of their blood pressure levels. Gu et al (2012) used this definition in their report showing that in the 2009-2010 National Health and Nutrition Examination Survey (NHANES) 75.7% of hypertensive adults aged 40 to 59 years and 83.6% of hypertensive adults aged ≥60 years used blood-pressure-lowering medication. In the derived variable dictionary for the ARIC study this same definition is used for the variable “hypertension”, and this definition of hypertension has been used in numerous publications that use ARIC data (e.g., Sturgeon et al., 2007).

A large number of studies have shown that hypertension is associated with increased risk of CVD and that control of blood pressure with anti-hypertensive medications reduces risk compared to untreated hypertension (MacMahon et al., 1990; Collins et al., 1990). There is surprisingly little literature comparing rates of CVD in individuals with medication-controlled blood pressure compared to un-medicated normotensives. We know of no studies that have directly tackled the questions of whether blood pressure normalized by medication in overweight and obese individuals is associated with the same stroke and CHD risk as that seen in normal weight individuals whose blood pressures are in the normal range without medication. This comparison is relevant to understanding the answer to the question, why worry about controlling weight to prevent hypertension, stroke and CHD when I can just take a pill to control the hypertension? Below we briefly review studies we have identified that address stroke and CHD risk by blood pressure and anti-hypertensive medication subgroups.
Perhaps the most relevant study was published by Liu et al. in 2015. The investigators used data from the Multi-Ethnic Study of Atherosclerosis (MESA) to examine the 9.5-year stroke and CHD risk in subgroups by blood pressure category and medication status. The 5798 American participants studied were ≥ 50 years at baseline. In multivariable-adjusted models that included BMI as well as 8 other covariates, the investigators showed that among participants with blood pressure <120/80 mmHg, the HR for CHD was 2.02 (95% CI: 1.37-2.97) and the HR for stroke was 2.56 (95% CI: 1.25-5.28) for medicated compared to un-medicated participants. Analysis by BMI groupings were not shown.

Zhang et al. (2012) evaluated the joint effects of healthy lifestyle factors, defined as having ≥3 of 5 healthy lifestyle factors (never smoking, normal weight, exercise, vegetable intake, light/moderate alcohol consumption), and antihypertensive treatment on (total) stroke risk in a Finnish population ages 25-74 (n=36,686). During a mean follow-up of 13.7 years men (HR=1.57; 95% CI: 1.17-2.11) and women (HR=2.25; 95% CI: 1.75-2.90) with antihypertensive medications and blood pressure <160/95 mm Hg had elevated adjusted total stroke hazards compared to adults in the same blood pressure category with no antihypertensive medications. The fully adjusted models included age, study year, education, and family history of stroke. These analyses were repeated after stratifying by ≥3 vs <3 risk factors, but data were not evaluated within BMI categories.

Asayama et al. (2009) studied 11,371 Japanese adults (ages 40-89 years) and found that compared to adults with optimal blood pressure (<120/80 mmHg) and no antihypertensive medications, antihypertensive-treated adults with “normal” blood pressure (120/80-129/84 mmHg) had elevated stroke rates (Table 1). Data were not evaluated by BMI categories.

Table 1. Adjusted relative hazard rates for first stroke by categories of blood pressure

<table>
<thead>
<tr>
<th>Categories</th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
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<tr>
<td></td>
<td>Events</td>
<td>RH</td>
<td>95% CI</td>
<td>Events</td>
<td>RH</td>
<td>95% CI</td>
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<tr>
<td>Unreated</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>5</td>
<td>1.00</td>
<td>N/A</td>
<td>9</td>
<td>1.00</td>
<td>N/A</td>
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<tr>
<td>Normal</td>
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<td>1.15-6.89</td>
<td>12</td>
<td>1.49</td>
<td>0.63-3.54</td>
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<tr>
<td>High normal</td>
<td>18</td>
<td>2.98</td>
<td>1.09-8.11</td>
<td>20</td>
<td>2.18</td>
<td>0.99-4.90</td>
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<tr>
<td>Grade 1 HT</td>
<td>34</td>
<td>5.83</td>
<td>2.27-15.0</td>
<td>28</td>
<td>3.01</td>
<td>1.40-6.45</td>
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<td>15</td>
<td>6.11</td>
<td>2.10-17.0</td>
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<td>6.20</td>
<td>2.77-13.9</td>
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<tr>
<td>Grade 3 HT</td>
<td>10</td>
<td>15.2</td>
<td>5.11-44.9</td>
<td>3</td>
<td>4.93</td>
<td>1.32-18.4</td>
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<td>5.11-44.9</td>
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<td>6.69</td>
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<td>14</td>
<td>4.89</td>
<td>2.06-11.7</td>
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<td>4.72-31.9</td>
<td>24</td>
<td>3.79</td>
<td>1.71-8.39</td>
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<tr>
<td>Grade 2 HT</td>
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<td>8.9</td>
<td>3.12-25.2</td>
<td>11</td>
<td>3.48</td>
<td>1.40-8.83</td>
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<tr>
<td>Grade 3 HT</td>
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<td>10.6</td>
<td>3.01-37.0</td>
<td>9</td>
<td>14.7</td>
<td>5.65-58.0</td>
</tr>
</tbody>
</table>

*Asayama et al., 2009. Reference group =untreated optimal blood pressure; “optimal” ≤120/80 mmHg; “normal” = 120/80-129/84 mmHg; “high normal” = 130/85-139/89 mmHg; “grade 1 HT” = mild hypertension; 140/90-159/99 mmHg; “grade 2 HT” = moderate hypertension; 160/100-179/109 mmHg; “grade 3 HT” = severe hypertension; ≥180/110 mmHg
Two publications from the Malmö Diet and Cancer (MDC) study in the southern region of Sweden provide further evidence for residual elevated stroke risk in hypertensives who control their blood pressure. Li et al. (2005, “Blood Pressure Control…”) assessed first-ever strokes in treated hypertensive participants. The proportion of strokes in antihypertensive-treated participants with controlled blood pressure (<140/90 mmHg) was 1.6% (7/450). The stroke rate was 289 per 100,000 person-years (95% CI, 75-504). In a separate publication Li et al. (2005, “Risk Factors for Stroke …”) assessed stroke risk in subjects with controlled blood pressure and no treatment for hypertension. The proportion of strokes in these normotensive, untreated participants was 0.5% (56/10,983), and the stroke rate was 90 per 100,000 person years (95% CI, 68-117). Putting this information together it appears that participants with controlled medicated blood pressure were at higher risk than normotensive (without medication) participants, but the authors did not make any formal comparisons between the groups studied in the 2 separate papers.

One ARIC study published in 1996 by Liao et al. compared participants taking antihypertensive medication with healthy participants who were not on antihypertensive medications; however, the outcome of interest was white matter lesion severity and obesity was not considered.

In summary, although a handful of studies have examined stroke, CHD and/or CVD risk by categories of blood pressure level and anti-hypertensive medication categories, we know of none that have also examined the impact of BMI on events by blood pressure control status and anti-hypertensive medication status. We think that this examination will give insight into the need for prevention of high blood pressure and the roles of weight control and antihypertensive medications.

5. Main Hypothesis/Study Questions:

We will have 3 outcomes – stroke, CHD and CVD. Each of these will be examined in a series of similar, but separate models.

Primary hypotheses: Risk of event will be different in the 12 groups (see below) formed by blood pressure, anti-hypertensive medication status and BMI category.

Secondary hypotheses to be examined in group contrasts:
1. Risks of stroke, CHD and CVD are higher in overweight and obese adults with blood pressure controlled by medication compared to normal weight participants who are normotensive (without high blood pressure and not taking anti-hypertensive medication).
2. Among adults with blood pressure controlled by medication, risks of stroke, CHD and CVD are higher in the overweight and obese compared to the normal weight if analyses are not adjusted for other cardiometabolic risk factors. The adjusted analyses will find weak or no difference.
3. Among normotensive adults, risks of stroke, CHD and CVD are higher in the overweight and obese compared to the normal weight if analyses are not adjusted for other cardiometabolic risk factors. The adjusted analyses will find weak or no difference.

6. **Definition**

The following abbreviations and terminology will be used in this section:

- **HT** – Hypertension – SBP/DBP ≥140/90 mmHg (≥130/80 mmHg for diabetic participants) or on antihypertensive medication
- **NBP** – Normal blood pressure – SBP/DBP <140/90 mmHg (<130/80 mmHg for diabetic participants) without antihypertensive medication
- **CMHT** – Controlled medicated hypertension – SBP/DBP <140/90 mmHg (<130/80 mmHg for diabetic participants) with antihypertensive medication
- **UMHT** – Uncontrolled medicated hypertension – SBP/DBP ≥140/90 mmHg (≥130/80 mmHg for diabetic participants) with antihypertensive medication
- **UUHT** – Uncontrolled, unmedicated hypertension – SBP/DBP ≥140/90 mmHg (≥130//80 mmHg for diabetic participants) with no antihypertensive medication

We will explore the use of thiazide, BB, CCB, ACEI, AT2RB, vasodilator and similar codes to capture antihypertensive medication exposure more accurately.

- **NWT** – Normal weight BMI 18.5-24.99 kg/m²
- **OWT** – Overweight BMI 25-29.99 kg/m²
- **OB** – Obese BMI ≥30 kg/m²

**Key exposure variable:** Categorical variable with 12 categories

- NWT NBP
- NWT CMHT
- NWT UMHT
- NWT UUHT
- OWT NBP
- OWT CMHT
- OWT UMHT
- OWT UUHT
- OB NBP
- OB CMHT
- OB UMHT
- OB UUHT
Outcomes: Incident Ischemic or Hemorrhagic Stroke, CHD, CVD

Stroke – definite/probable incident stroke (ischemic or hemorrhagic) by censoring date
CHD – hospitalized myocardial infarction (MI), fatal CHD, or silent MI by censoring date
CVD – stroke and CHD

Study Design and Analysis
Our study design is adapted from that used by Hernán et al. (2008) and is guided by elements of mimicking an intention-to-treat (ITT) analysis as a randomized trial while using observational data (see Figure 1). Briefly, this method treats the observational cohort as a sequence of nonrandomized “nested trials”. In the text below we summarize our analysis plans for the primary hypothesis.

Exclusions: We will apply the routine ARIC sampling exclusions and exclusions for missing key variables. Underweight participants will be excluded as the causes of underweight are complex and the group is not pertinent to our primary hypothesis. In our design participants are eligible to contribute follow-up time in a single “trial” if they are free of CVD and report no anti-hypertensive medication therapy at the prior ARIC visit. If the data are assumed to be valid and there are no changes in medication status other than those captured, all medication users are new users over a 3 year period. Participants who do not meet that criteria are excluded from that trial.

Analytic approach: Using visit 1 through visit 4 data and events up to December 31, 2013 (or the latest available), we will conduct three “trials” and then pool those data to estimate adjusted average hazard ratios for our outcomes of interest (see Figure 1). The first trial will start at visit 2, and it will include participants who report no anti-hypertensive medication therapy at visit 1 and no prior events; the second trial will start at visit 3, and it will include participants who report no anti-hypertensive medication therapy at visit 2 and no prior events; the third trial will start at visit 4, and it will include participants who report no anti-hypertensive medication therapy at visit 3 and no prior events. Anti-hypertensive medication initiators will be defined as individuals who report medication use at the beginning of the trial, but no reported medications at the prior visit date. Follow-up time for medication initiators will begin on the visit date for which they are reporting medication use—after the prior visit of no reported use. Anti-hypertensive medication non-initiators will be defined as individuals who report no medication use at the beginning of the trial, and no reported medications at the prior visit. Follow-up time for medication non-initiators will begin on the second consecutive visit date for which they are reporting no medication use. Under the ITT approach, we will record BMI category, medication status and blood pressure control status at the beginning of each trial, and we will track follow-up time until 1) an event, 2) loss to follow-up, or 3) administrative censoring on December 31, 2013 (or the latest available date). Because some individuals may participate in more than one trial, we will use a robust variance estimator to account for within-person correlation.
We will test overall models to identify any differences between categories using survival analysis (PROC PHREG in SAS). If the overall test is significant, we will examine specific contrasts as laid out in our secondary hypotheses. The reference group will be normal weight adults with normal blood pressure (NWT NBP). We recognize that our analyses could have been conducted with interaction terms rather than with the creation and analysis of 12 categories; however, we feel that the latter approach has the advantage of allowing us to directly and simply test difference between the subgroups that are of most interest to us.

Covariates to be included are age, sex, race/ARIC site, education, physical activity, smoking and alcohol consumption. Additional variables to be examined and considered for inclusion in some models are hormone use, diet (% calories from fat, saturated fat, simple sugars), blood pressure, diabetes status, dyslipidemia, family history of CVD.

Analyses will be repeated to study each outcome. Because some participants could die from causes other than CVD, we will run a competing risk analysis as a sensitivity analysis.

Methodologic Limitations or Challenges
A methodologic limitation is that Medicare Part D data or administrative claims data are not available in visits 1 through 4 to determine the adherence and persistence of anti-hypertensive medication use. Medication data in the ARIC study is reported at each of the first 4 visit as recent prescriptions used in the past two weeks. This form of data collection leaves a very small window of time to measure medication exposures which are then assumed to be constant over the subsequent three-year period between Exam visits. This long period between medication reassessments is problematic because it may miss medications that are used intermittently, and because there is poor measurement of medication adherence and persistence up through visit 4. Over the course of one year, it has been reported that 30 to 40% of antihypertensive medication monotherapy initiators discontinue treatment (Elliott et al., 2007). Poor measurement of medication-taking behavior may lead to varying degrees of exposure misclassification which is particularly concerning for chronic disease medication exposures. Additionally, in our “new user” design, we are unable to precisely determine the exact time of medication initiation within the 3-year period between exam visits. We will explore this through a sensitivity analysis that assigns the date of medication initiation as the midpoint between the visit for which medications are reported and the prior visit for which there is no reported use of medication.

The generalizability of our proposed study may be affected because the medication regimens used by the ARIC population may be different from those that are currently used. We will explore this by assessing the anti-hypertensive medication classes that are most reported at each visit. Furthermore, due to sample size limitations, our design is unable to incorporate an incident overweight/obese population that subsequently develops uncontrolled blood pressure.
Figure 1. Design layout for ARIC Study: Participants who do not meet the eligibility criteria for a “trial” will not be included in that trial, but can be included in subsequent trials. Medication status is a determinant of eligibility. The primary exposure variables includes 12 groups, each of which has medication status designated.
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.cscu.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)?

    Chambless LE, Shahar E, Sharrett AR, Heiss G, Wijnberg L, Paton CC, Sorlie P, Toole
    JF. Association of Transient Ischemic Attack/Stroke Symptoms Assessed by
    Standardized Questionnaire and Algorithm with Cerebrovascular Risk Factors and

    Folsom AR, Rasmussen ML, Chambless LE, Howard G, Cooper LS, Schmidt MI, Heiss
    G. Prospective Associations of Fasting Insulin, Body Fat Distribution, and

    Juhaeri, Stevens J, Chambless LE, Tyroler HA, Rosamond W, Nieto FJ, Schreiner P,
    Jones DW, Arnett D. Associations between weight gain and incident


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/

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.
13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication.

Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript _____ Yes ___X__ No.

References


