1.a. **Full Title**: Prevalence of hypotension in older adults with and without antihypertensive medication use

   **b. Abbreviated Title (Length 26 characters)**: Hypotension Prevalence

2. **Writing Group**: Joe Coresh, Rebecca Gottesman (senior), Melinda Power (first), A. Richey Sharrett, others welcome

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

**First author**: Melinda Power
**Address**: Phipps 446D
600 North Wolfe Street
Baltimore, MD 21287
**Phone**: 617.721.9984 **Fax**: 410-955-0672
**E-mail**: melindacpower@gmail.com

**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**: Rebecca Gottesman
**Address**: Phipps 446D
600 North Wolfe Street
Baltimore, MD

**Phone**: 410-614-2381 **Fax**: 410-955-0672
**E-mail**: rgottesm@jhmi.edu

3. **Timeline**:

   We plan to submit for publication within 6 months of approval.

4. **Rationale**:

   Observational research and randomized trials provide strong evidence to support treating severe hypertension for the prevention of myocardial infarction, stroke, renal failure and death. Recent recommendation on the management of high blood pressure from the
Eighth Joint National Committee (JNC8) recommend different target systolic and diastolic blood pressure (SBP and DBP) levels according to age and co-morbidities. Target blood pressure levels of <140/90 mm Hg are recommended for persons under 60 years and all those with chronic kidney disease or diabetes, while levels of <150/90 are recommended for persons over 60 years. The slightly higher targets in older ages are a departure from the previous guidelines, resulting from low-quality evidence that setting a lower SBP goal does not result in clinical benefit.

In the United States, use of antihypertensive medications has been rising. According to analyses of data from the National Health and Nutrition Examination Surveys, the prevalence of antihypertensive medication use rose from 64% in 2001 to 77% in 2009-2010. The number of persons using multiple antihypertensive agents also rose during this time period, from 37% to 48%. Furthermore, as may be expected given the rise in the prevalence of antihypertensive medication use, the percent of persons with controlled hypertension, typically defined in prior research as blood pressures <140 mmHg systolic and <90 mm Hg diastolic (or <130/80 for persons with diabetes or chronic kidney disease), also rose during this period, from 29% to 47%. However, attempts to achieve controlled hypertension often results in diastolic hypotension. For example, aggressive treatment with an aim achieve a goal blood pressure of <130/85 mm Hg in hypertensive diabetic patients resulted in 57% of patients with a diastolic blood pressure ≤70 mm Hg, despite reductions in SBP to target levels in only about a third of patients. Similarly, hypotension was also common in treated hypertensive chronic kidney disease patients.

Many physicians consider low blood pressure to be a problem only if it produces noticeable symptoms. However, there are concerns that hypotension, especially diastolic hypotension can also be dangerous, particularly among older adults with prior cardiovascular disease.

Hypotension in later years may lead to a variety of cardiovascular outcomes. Higher pulse pressure, which may reflect isolated SBP and isolated diastolic DBP or both elevated SBP and depressed DBP, predicts cardiovascular outcomes. For example, in the Framingham Heart Study, low DBP was associated with increased risk of coronary heart disease in the presence of elevated SBP, especially at older ages. However, isolated diastolic hypotension may also predict cardiovascular disease risk. In a cohort of older adults, isolated diastolic hypotension was associated with higher incidence of heart failure.

The potential impact of hypotension on brain health is particularly troubling. For example, in data from both the Bronx Aging Study and Kungsholmen Project, low late-life DBP was associated with increased risk of subsequent dementia, and in data from the Honolulu-Asia Aging Study, low midlife DBP was marginally associated with increased dementia risk. Similar associations are observed between low blood pressure and worse cognitive function. In addition, cross-sectional epidemiologic analyses in the Rotterdam Study suggest increased severity of periventricular white matter hyperintensities (WMH), suggestive of small vessel disease in the brain, with both high and low concurrent DBP among persons with prior myocardial infarction. Conversely
there was no increased risk among those without prior myocardial infarction. In pooled data from several European cohorts, both prior increase and decrease in diastolic blood pressure was associated with increased risk of severe WMH at follow-up. However it must be noted that there was no report of an association between prior or concurrent low blood pressure and WMH progression in ARIC. While multiple non-causal explanations may account for these associations, including the possibility of an impact of poor brain health or prior hypertension on blood pressure levels, rather than the reverse, the possibility that chronic hypoperfusion and related ischemia due to hypotension promotes small vessel disease and dementia pathogenesis remains plausible and cannot be discounted.

Hypertension followed by hypotension may be particularly detrimental to cardiovascular and brain health. RCTs of aggressive blood pressure lowering, by their nature, reduce blood pressure in hypertensive persons to levels likely to result in transient or chronic hypotension, particularly diastolic hypotension. Several trials of aggressive blood pressure lowering, including SHEP and INVEST, have noted increased cardiovascular risk with lower blood pressure, although there are exceptions (e.g., HYVET). Trial evidence linking antihypertensive medication use to cognitive benefit in persons without overt cerebrovascular disease is weak, although potentially biased due to differential attrition, disallowing strong conclusions. Interestingly, in observational data from the AGES-Reykjavik Study, participants with a history of midlife hypertension and low late-life DBP exhibited smaller total and gray matter brain volumes as well as lower memory scores than their peers.

Given growing concerns about adverse consequences of hypotension, an understanding of the prevalence of hypotension, and in particular medication-induced hypotension, is crucial. Nevertheless, reports of the prevalence of hypotension in the general population, and specifically in older adults who may be at greatest risk of adverse effects, are generally lacking. Large studies reporting on prevalence of trends in blood pressure and antihypertensive medication use typically report only on hypertension and control of hypertension. The single report we were able to identify considered data from prior to the 2000 and excluded persons with anti-hypertensive medication use. As such, the current prevalence of hypotension in older is unknown, and it is unclear whether aggressive treatment of hypertension is leading to a rise in the number of treated older adults with hypotension. The objective of this proposal is to evaluate the prevalence of hypotension in older adult participants of ARIC and to examine whether this prevalence is increasing or decreasing over time.

5. Main Hypothesis/Study Questions:

The aim of this report is to describe the current prevalence of hypotension ARIC participants with and without use of anti-hypertensive medications and the frequency with which formerly hypertensive individuals become hypotensive in later life. We will also address whether the prevalence of hypotension has changed in the past 10 years, given greater emphasis on blood pressure control, and relate hypotension prevalence to prevalence of elevated hs-troponin, NT-pro-BNP or dementia.
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:**
This is a descriptive study. First, we will examine the prevalence of hypotension in older persons, overall and after additional consideration of antihypertensive medication use, using data from ARIC Visits 1 (1987-1989), 4 (1996-1998), and 5 (2011-2013). Second, we will describe the prevalence of patterns of achieved blood pressure over time, with particular emphasis on understanding the prevalence of persons with elevated blood pressure in midlife (ARIC Visits 1 and/or 4) who currently exhibit hypotension (ARIC Visit 5). Finally, for comparative purposes, we will compare standardized prevalence of hypotension, from Visit 4 and Visit 5, using participants ages 68-73 at each study visit (as this is an aging cohort, this range corresponds to the overlap in ages considered at the two study visits – at Visit 4, 2,540 participants were ages 68-73, while at visit 5, 2,888 met these age criteria).

**Variables of Interest:**

At each study visit study personnel measured systolic and diastolic blood pressure (SBP and DBP) up to three times using a random zero mercury (Visits 1, 4) or automatic (Visit 5) sphygmomanometer, according to a standardized protocol including 5 minutes of rest preceding each measurement; we used the mean of the two final measurements to characterize blood pressure at each visit. Antihypertensive medication use was determined through direct visual inspection of all current prescription and over-the-counter medications at each study visit. We classified medications as antihypertensive medications using Medi-Span Therapeutic Classification codes.

We will classify hypo/normo/hypertension according to the following cut-offs:

<table>
<thead>
<tr>
<th></th>
<th>Hypotensive</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>&lt;110 mm Hg</td>
<td>110-139 mm Hg</td>
<td>≥140 mmHg</td>
</tr>
<tr>
<td>DBP</td>
<td>&lt;60 mm Hg</td>
<td>60-90 mm Hg</td>
<td>≥90 mmHg</td>
</tr>
<tr>
<td>SBP/DBP</td>
<td>&lt;110/60 mm Hg</td>
<td>110-139/60-90 mm Hg</td>
<td>≥140/90 mmHg, neither SBP or DBP considered hypotensive</td>
</tr>
</tbody>
</table>

We will further evaluate the prevalence of persons with systolic hypertension and diastolic hypotension, and may treat this as a separate group given large enough numbers.

We will further classify persons into one of six groups (listed below) based on their measured systolic blood pressure (SBP), diastolic blood pressure (DBP), or combined SBP and DBP:
1. Hypotensive, No anti-hypertensive medication use
2. Hypotensive, Anti-hypertensive medication use
3. Normotensive, No anti-hypertensive medication use
4. Normotensive, Anti-hypertensive medication use
5. Hypertensive, No anti-hypertensive medication use
6. Hypertensive, Anti-hypertensive medication use

Finally, we will classify persons according to patterns of achieved blood pressure and medication use from Visits 1 and/or 4 to Visit 5. Initially, we will consider cross classification using the 6-level blood pressure/medication use variable above, but will collapse categories or otherwise summarize patterns to aid interpretability. Particular attention will be paid to identifying and understanding the prevalence of persons with prior hypertension and current hypotension.

In addition, we will consider hs-troponin, NT-pro-BNP, and dementia status at Visit 5.

**Subgroups of Interest:** Groups based on gender, race, age, education, study site, and prevalent diabetes, chronic kidney disease, and coronary heart disease.

**Statistical Analyses:** We will tabulate Visit 1, 4, and 5 data on demographic characteristics of the sample, the prevalence of hyper/normo/hypertension, our six-level blood pressure/antihypertensive medication use variable, and our cross-classification denoting patterns of achieved blood pressure with or without medication use, overall and within subgroups of interest. We will also compute mean (SD) and median SBP and DBP for each category, overall and within subgroups of interest. To provide insight into whether the prevalence of hypotension in older adults (with or without antihypertensive medication use) is rising or falling, we will compare prevalence estimates using data from the subset of persons aged 68-73 at Visit 4 and Visit 5, standardized to Visit 5 distributions of age, gender, race, education, study site, and disease status (diabetes, chronic kidney disease, cardiovascular disease). The use of the narrow age range is necessary given the minimal overlap in ages considered at Visits 4 and 5 in this aging cohort. We will also use linear and logistic regression to relate hypotension at each visit and the pattern of blood pressure (e.g. hypertensive in midlife, hypotensive in late life) over ARIC visits to hs-troponin, NT-pro-BNP, and dementia.

**Limitations/Challenges:**

We recognize that ARIC is not a representative U.S. population; data from ARIC covers a limited range of ages and includes only black and white participants from four U.S. communities. However, we expect our results to be sufficient to indicate whether hypotension is common or uncommon in the older adult U.S. population among persons with and without antihypertensive medication use. In addition, heterogeneity across site is in itself of potential interest, given the potential for regional differences in demographics and health-related conditions predicating blood pressure control as well as differences in blood pressure management practices across the country. We consider the
prevalence of hypotension by antihypertensive medication use but will not consider the impact of non-pharmacologic treatment of hypertension on hypotension prevalence. Our assessment of blood pressure was conducted at a single study visit. Given within-person physiologic variability in blood pressure, we may have misclassification of hypotension status. However, given use of the average of two readings and reported findings that hypertension prevalence was similar when estimated from a single measurement or the average of 6 measurements across two visits, we do not expect to significantly impact our findings. Of more concern is the possibility of “white coat hypertension” which may lead to an underestimate of hypotension in our sample. While use of ambulatory blood pressures may bypass this potential uses, we do not currently have access to such data.

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.csc 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)?

#2178 – Miedema - Prevalence and control of hypertension and hyperlipidemia and use of preventative cardiovascular medications in a US cohort, the Atherosclerosis Risk in Communities Study

#114 – Neito – Blood pressure distributions
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: ARIC NCS: 2008.06)

   ____ 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.cscce.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.cscce.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.

References