1.a. **Full Title**: Single versus multiple blood pressure measurements: reclassification and subsequent risk of incident hypertension, cardiovascular disease, and death

b. **Abbreviated Title (Length 26 characters)**: Single & multiple BP measurements

2. **Writing Group**: Writing group members: Yifei Lu, Olive Tang, Edger Miller, Gerardo Heiss, Lawrence Appel, Kunihiro Matsushita

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

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3. **Timeline**: The analyses will use existing ARIC data, and manuscript preparation will be performed in the following 6 months after manuscript proposal approval.

4. **Rationale**:  

Despite the availability of evidence-based treatment options, hypertension is still the leading modifiable risk factor for mortality worldwide.\(^1\) Accurate measurement of blood pressure (BP) is essential to properly diagnose and manage hypertension. Since BP can be highly variable due to physiological variation and/or measurement methods,\(^2\) clinical guidelines recommend measuring BP multiple times at a single visit and recording their average (e.g. average of last two out of three measurements).\(^3,6\) On the other hand, in real world clinical practice, it is often not practical to obtain multiple measurements of BP, particularly in limited resource settings (e.g., relative shortage of healthcare providers).\(^7\)
In this context, interestingly, a previous study using data from the National Health and Nutrition Examination Survey (NHANES) demonstrated that a reclassification by the average of the last two measurements from the first BP occurred in small proportion (10%-20%) of participants. This raises a possibility that a single BP measurement may be acceptable in some patients or in certain scenarios.

To more comprehensively tackle this issue, we propose to evaluate reclassification of BP categories across different options using single vs. multiple BP (e.g., 1st or 2nd vs. average of all three or 2nd and 3rd) in the Atherosclerosis Risk in Communities (ARIC) Study. We will also explore any demographic and clinical characteristics related to the reclassification of BP categories. Furthermore, leveraging long-term follow-up in ARIC, we will assess prognostic implications of BP reclassification between single vs. multiple BP. To make our findings globally applicable, we will first utilize the classic hypertension definition of BP \( \geq 140/90 \). We will then repeat the analysis with new BP categories proposed in the 2017 AHA/ACC guidelines.

5. Main Hypothesis/Study Questions:

1) Reclassification of hypertension across several combinations of single vs. multiple BP (e.g., 1st vs. average of 2nd and 3rd)

2) Characteristics related to reclassification of BP categories

3) Prognostic implications of BP reclassification

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:

We will conduct a cross-sectional analysis for the reclassification of hypertension, and a prospective analysis of BP reclassification and subsequent risk of incident hypertension, cardiovascular disease (CVD), and death.

Inclusion criteria:

All black and white ARIC study participants at visit 1.

Exclusion criteria:

<table>
<thead>
<tr>
<th>Cross-sectional</th>
<th>Prospective</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>For analysis of incident hypertension: self-reported hypertension based on doctor diagnosis, medication use, or measured systolic BP (SBP) ( \geq 140 \text{mmHg} ) or diastolic BP (DBP) ( \geq 90 \text{mmHg} ) based on average of last two readings at baseline.</td>
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</tr>
<tr>
<td>2</td>
<td>Self-identified non-white/non-black</td>
</tr>
<tr>
<td>3</td>
<td>Missing data on BP measurements, anti-hypertensive mediation, and covariates of interest</td>
</tr>
<tr>
<td>4</td>
<td>Missing data on incident hypertension, CVD, or all-cause mortality in the respective analyses</td>
</tr>
</tbody>
</table>

**BP at visits 1-5:**

The sitting arm BP was measured by a certified trained technician. ARIC participants were requested not to smoke, eat, exercise, or expose to cold temperature at least 30 minutes before measurements. After five minutes of quiet rest, three readings at one-minute interval were recorded using a standardized Hawksley random-zero sphygmomanometer at visits 1-3. Only two measurements were performed at visit 4. At visit 5, BP was measured three times with a validated automatic sphygmomanometer (the OMRON HEM-907 XL). After the first two measurements, participants were requested to raise cuffed arm above head for five seconds, then return to the original resting position and take the 3rd measurement.

At each visit, whether “having high blood pressure or hypertension ever diagnosed” or “taking anti-hypertension medication within the past 2 weeks” were asked to report by cohort participants.

**Main variables related to BP and hypertension:**

- Demographics: age, race, sex;
- Physical examination: body mass index, heart rate;
- Lab examination: total cholesterol, HDL cholesterol, estimated glomerular filtration rate;
- Lifestyle: education level, smoking status, drinking status;
- Comorbidities: diabetes, CVD;
- Medication: cholesterol-lowering medication

**Outcomes for prospective analysis:**

Incident hypertension, incident CVD (including the first occurrence of either coronary heart disease, stroke, or heart failure, whichever came first), and all-cause mortality were ascertained via follow-up visits, annual follow-up contacts (semi-annual follow-up contacts after 2012), community-wide hospital surveillance, and death certificates from state vital statistics office. Specifically, we defined incident hypertension as either newly self-reported hypertension (doctor diagnosis or medication use) or newly measured hypertension (SBP/DBP ≥140/90 mmHg based on average of last two readings). Incident coronary heart disease was defined as a definite or probable myocardial infarction, or fatal coronary heart disease. Incident stroke was identified as definite or probable ischemic and hemorrhagic stroke cases, defined as sudden or rapid onset of neurological symptoms that lasted for 24 hours or led to death in the absence of another cause. Incident heart failure was defined as the first occurrence of a hospitalization that included an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) discharge diagnosis code for heart failure beginning with “428” in any position, or a death certificate ICD-9 code beginning with “428”, or ICD-10 code “I50” in any position.
Participants without any outcomes will be censored at last semi-annual follow-up, or December 31, 2016.

Statistical analysis:

Cross-sectional analysis:

As noted above, hypertension will be primarily defined as SBP/DBP ≥140/90 mmHg but we will also explore SBP/DBP ≥130/80 mmHg according to 2017 AHA/ACC hypertension guidelines. All analyses will be done separately between participants with and without clinical diagnosis of hypertension (the former and the latter will have implications on hypertension management and screening, respectively). We will quantify the proportion of participants who will be reclassified by several combinations of simpler vs. conventional approaches (see table below).

<table>
<thead>
<tr>
<th>#</th>
<th>Simpler approach (mostly single BP)</th>
<th>Conventional (or “gold standard”)</th>
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<tbody>
<tr>
<td>1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; BP</td>
<td>Average of 2&lt;sup&gt;nd&lt;/sup&gt; and 3&lt;sup&gt;rd&lt;/sup&gt; (gold standard in guidelines and many research studies)</td>
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<tr>
<td>2</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; BP</td>
<td>Average of 1&lt;sup&gt;st&lt;/sup&gt; and 2&lt;sup&gt;nd&lt;/sup&gt; (gold standard for visit 4)</td>
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<tr>
<td>3</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; BP</td>
<td>Average of all three (gold standard in several trials)</td>
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<tr>
<td>4</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; BP</td>
<td>Average of 2&lt;sup&gt;nd&lt;/sup&gt; and 3&lt;sup&gt;rd&lt;/sup&gt; (gold standard in guidelines and many research studies)</td>
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<tr>
<td>5</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; BP</td>
<td>Average of 1&lt;sup&gt;st&lt;/sup&gt; and 2&lt;sup&gt;nd&lt;/sup&gt; (gold standard for visit 4)</td>
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<tr>
<td>6</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; BP</td>
<td>Average of all three (gold standard in several trials)</td>
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<tr>
<td>7</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; if &lt;140/90 and 2&lt;sup&gt;nd&lt;/sup&gt; if first BP ≥140/90</td>
<td>Average of 2&lt;sup&gt;nd&lt;/sup&gt; and 3&lt;sup&gt;rd&lt;/sup&gt; (gold standard in guidelines and many research studies)</td>
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<tr>
<td>8</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; if &lt;140/90 and 2&lt;sup&gt;nd&lt;/sup&gt; if first BP ≥140/90</td>
<td>Average of 1&lt;sup&gt;st&lt;/sup&gt; and 2&lt;sup&gt;nd&lt;/sup&gt; (gold standard for visit 4)</td>
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<tr>
<td>9</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; if &lt;140/90 and 2&lt;sup&gt;nd&lt;/sup&gt; if first BP ≥140/90</td>
<td>Average of all three (gold standard in several trials)</td>
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<tr>
<td>10</td>
<td>Average of 1&lt;sup&gt;st&lt;/sup&gt; and 2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>Average of 2&lt;sup&gt;nd&lt;/sup&gt; and 3&lt;sup&gt;rd&lt;/sup&gt;</td>
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<tr>
<td>11</td>
<td>Average of 1&lt;sup&gt;st&lt;/sup&gt; and 2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>Average of all three (gold standard in several trials)</td>
</tr>
</tbody>
</table>

We will additionally explore reclassification across categories below the diagnostic threshold for hypertension (e.g., normal, elevated BP, or prehypertension) proposed in several major guidelines like JNC7 and the AHA 2017 AHA/ACC guidelines (e.g., <120/80 and 120-139/80-89 in JNC7). Subsequently, we will systematically explore demographic and clinical factors related to the reclassification in the scenarios 1-11 shown above using multinomial logistic regression with upward reclassification (from non-hypertension to hypertension), no reclassification, and downward reclassification (from hypertension to non-hypertension) as outcome variables.

Prospective analysis:
Again, we will perform the analysis in those with and without hypertension diagnosis, separately. For the analysis of incident hypertension, we will exclude those with diagnosed hypertension or baseline SBP/DBP $\geq 140/90$ mmHg based on average of last two readings. Similarly, for the analysis of incident cardiovascular outcomes, we will exclude those with history of CVD at baseline.

We will primarily evaluate the risk of clinical outcomes of interest across cross-categories of hypertension status in the scenarios #1-11 shown in the table above (e.g., for the scenario #1: non-hypertension in both 1st BP and the average of 2nd and 3rd, hypertension in 1st alone, hypertension in the average of 2nd and 3rd alone, vs. non-hypertension in both 1st BP and the average of 2nd and 3rd). Then we will extend to cross-categories below hypertension (e.g., elevated BP). We will use Cox proportional hazard models to quantify the associations of cross-categories of BP and account for covariates in a graded manner: model 1 without covariates (crude), model 2 adjusting for age, gender, and race, and model 3 additionally adjusting for education level, smoking and drinking status, body mass index, heart rate, total and high-density lipoprotein cholesterol, cholesterol-lowering medication, estimated glomerular filtration rate, and prevalent diabetes. For the analysis of incident hypertension and mortality, we will also adjust for prevalent CVD in model 3.

For both cross-sectional and prospective analyses, we will evaluate overall and by some key subgroups according to age, gender, race, smoking status, diabetes, CVD, and chronic kidney disease (reduced glomerular filtration rate and/or elevated albuminuria [when applicable]). We will primarily analyze BP at visit 1 but explore whether we obtain consistent results using data from visits 2-5. When results are not consistent in some specific visits, we will consider some methodological aspects in some visits (e.g., only two BP measurements at visit 4, an oscillometric device was used at visit 5), and that participants are older at later visits. All analyses will be performed with Stata version 14.0, and a p-value $<0.05$ will be considered statistically significant.

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)?

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
   ___   A. primarily the result of an ancillary study (list number* _________)
   ___X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _2014.05__ __________ __________)

*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, approved manuscripts using 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 ____ No.

References: