1.a. **Full Title:** Comparison of very high-risk conditions in the 2018 AHA/ACC cholesterol guideline regarding secondary adverse outcomes among patients with atherosclerosis cardiovascular disease

   **b. Abbreviated Title (Length 26 characters):** Clinical factors in the guideline and secondary outcomes in ASCVD

2. **Writing Group:**
   Writing group members: Yejin Mok, Shoshana H. Ballew, Anna Kucharska-Newton, Silvia Koton, Josef Coresh, Wayne Rosamond, Kunihiro Matsushita; others welcome

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

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3. **Timeline:** Analyses and manuscript preparation will be performed over the next 6 months.

4. **Rationale:**
   Although cardiovascular risk prediction has been mainly discussed in the context of primary prevention, given the availability of a new, effective but expensive lipid-lowering medication,
proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, the AHA/ACC 2018 Cholesterol Guideline has brought a new concept of “very high-risk” and “high-risk” for patients with prior atherosclerotic cardiovascular disease (ASCVD). Specifically, the Guideline proposes using an LDL-C threshold of 70 mg/dL to consider the use of ezetimibe and PCSK9 inhibitors for ASCVD patients at “very high-risk” of events defined as multiple major ASCVD events (i.e., acute coronary syndrome within 12 months, a history of myocardial infarction, ischemic stroke, or symptomatic peripheral artery disease) or 1 major ASCVD event plus multiple high-risk conditions (e.g., hypertension, current smoking, diabetes, reduced kidney function). However, these criteria for “very high-risk” are not necessarily evidence-based and are based on inclusion criteria of clinical trials testing the efficacy of PCSK9 inhibitors.

Therefore, we will quantify the association of “very high-risk” vs. “high-risk”, defined according to the AHA/ACC guidelines, with secondary adverse outcomes among participants with a history of ASCVD using the Atherosclerosis Risk in Communities (ARIC) study. We will evaluate subgroups within “very high-risk” according to the combination of prevalent major ASCVD events and the number of high-risk conditions in terms of prognosis. We will also compare individual high-risk conditions regarding the risk of secondary adverse outcomes.

5. Main Hypothesis/Study Questions:
- Study participants with a history of ASCVD and at “very high-risk” will have higher risk of adverse outcomes (all-cause mortality, cardiovascular mortality, MI, ischemic stroke or heart failure), compared to those at “high-risk”.
- There will be a risk gradient within “very high-risk” and “high-risk” according to the number and combination of prevalent major ASCVD events and high-risk conditions in patients with ASCVD.
- Each high-risk condition will be independently associated with adverse outcomes but in a different magnitude.

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: prospective cohort study
- We will quantify the association of “very high-risk” with the risk of adverse outcomes in study participants with a history of ASCVD. We will use visit 4 data for primary analysis, which has data on high-risk conditions (e.g., serum creatinine) and will allow us to explore a relatively large number of ASCVD cases at baseline and a ~20 years of follow-up. We will repeat the analysis using visit 5 to confirm the robustness of our findings and potentially different results in older adults.

Inclusions:
- All ARIC participants with a history of ASCVD and non-missing covariate date defining risk categories identified at relevant baseline visits (Table 2).

Exclusions:
- Individuals without ASCVD at study baseline (Visit 4)
- Race other than black and white
- Missing data on high-risk conditions and covariates of interest
- Missing outcome data

Exposures:
- **“Very high-risk”**: a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
- **Major ASCVD**
  Major ASCVD includes a history of myocardial infarction (MI), history of ischemic stroke and symptomatic PAD at study baseline. Major ASCVD will be defined as below (Table 1).

<table>
<thead>
<tr>
<th>Major ASCVD Events</th>
<th>Definition</th>
</tr>
</thead>
</table>
| History of MI            | • Self-reported MI or electrocardiogram (ECG) at visit 1  
  • Definite or probable MI cases adjudicated by ARIC physician panel in follow-up through Visit 4  |
| History of ischemic stroke| • Self-reported stroke at visit 1  
  • Definite of probable ischemic stroke cases adjudicated by ARIC physician panel in follow-up through Visit 4  |
| Symptomatic PAD          | • Self-reported history of leg revascularization or intermittent claudication  
  • Ankle-brachial index (ABI) <0.85 at visit 1 or visit 5  
  • Incident PAD, revascularization and amputation based on hospital discharge diagnosis and procedure codes (ICD-9: 440.2, 440.20, 440.21, 440.22, 440.23, 440.24, 440.29 440.3, 440.4, 38.18, 39.25, 39.29, 39.50, 84.1) |

- **High-risk conditions**
  High risk conditions in the current guideline include the following factors: age≥65 years, heterozygous familial hypercholesterolemia, history of prior coronary bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s), diabetes, hypertension, chronic kidney disease, current smoking, persistently elevated LDL-C despite maximally tolerated statin therapy and ezetimibe and history of congestive heart failure. However, since information on familial hypercholesterolemia is limited, we will not include this condition in our analysis. Each high-risk condition will be defined as below (Table 2).

<table>
<thead>
<tr>
<th>High-risk conditions</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
<td>Age at study baseline</td>
</tr>
<tr>
<td>Heterozygous familial hypercholesterolemia</td>
<td>Not available</td>
</tr>
<tr>
<td>History of prior CABG or PCI</td>
<td>Procedure codes prior to study baseline (ICD-9: 36.0, 36.1, 36.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Fasting/non-fasting glucose levels ≥126/140 mg/dL, self-reported doctor diagnosed diabetes, or diabetes medication use at study baseline</td>
</tr>
</tbody>
</table>
Hypertension: Systolic/diastolic blood pressure ≥140/90 mmHg, or hypertension medication use at study baseline

Chronic kidney disease: eGFR 15-59 ml/min/1.73m² at study baseline*

Current smoking: Current smoking at study baseline

Elevated LDL-C: LDL-C ≥2.6 mmol/L and statin use at study baseline

History of heart failure: Hospital discharge diagnosis (ICD-9: 428) prior to study baseline

*We will explore albuminuria as well

**Outcomes:**
- Composite and individual adverse outcomes of all-cause mortality, cardiovascular mortality, MI, ischemic stroke, and heart failure
  - Cardiovascular death will be defined as death from coronary heart disease, stroke, or heart failure
  - MI and ischemic stroke will be defined as definite or probable cases adjudicated by ARIC physician panel
  - Heart failure will be defined as hospitalization having in any position an ICD-9 code 428 for heart failure diagnosis

**Covariates:**
In addition to major ASCVD events and high-risk conditions in the guidelines, gender and race will be treated as covariates. We will, further, examine potential effect measure modification by gender and race. We will consider albumin to creatinine ratio (ACR), a measure representing kidney damage, which was emphasized as characterizing chronic kidney disease by the current international clinical guideline.³

**Statistical analysis**
1. We will summarize basic characteristics according to categories of “very high-risk” vs. “high-risk” (we will subdivide “very high-risk” if the sample size allows).
2. Cumulative incidence of adverse outcomes will be estimated by “very high-risk” vs. “high-risk” using the Kaplan-Meier method.
3. Subsequently, we will quantify the association of “very high-risk” and “high-risk” with adverse outcomes using Cox proportional hazards models. We will also assess the risk of adverse outcomes according to fine categories of “very high-risk” and “high-risk” (e.g., multiple ASCVD events vs. 1 ASCVD event+number of high-risk conditions).
4. We will examine the independent association of each high-risk condition with the risk of adverse outcomes. We will also examine the association of other risk conditions (e.g., albuminuria and atrial fibrillation) with adverse outcomes independently of other high-risk conditions.
5. We will conduct the following sensitivity analyses:
   a. We will repeat analysis in several subgroups by gender and race.
   b. We will repeat our analysis using visit 5 data to confirm the robustness of our findings.

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.cscs.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? ____ 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.cscs.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.cscs.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