1.a. **Full Title**: The association of clinically recognized varicose veins with incident cardiovascular disease in older individuals

b. **Abbreviated Title (Length 26 characters)**: Varicose veins and cardiovascular disease

2. **Writing Group**:
   Writing group members: Yejin Mok, Junichi Ishigami, Anna Kucharska-Newton, Maya Salameh, Priya Palta, Josef Coresh, B. Gwen Windham, Pamela Lutsey, Kunihiro Matsushita

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]

**First author**: Yejin Mok
**Address**: Welch Center for Prevention, Epidemiology, and Clinical Research
2024 E. Monument St., Baltimore, MD 21287

Phone: (443)960-5475	Fax: 
E-mail: ymok2@jhu.edu

**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**: Kunihiro Matsushita
**Address**: Welch Center for Prevention, Epidemiology, and Clinical Research
2024 E. Monument St., suite 2-600, Baltimore, MD 21287

Phone: (443)287-8766	Fax: (410)367-2384
E-mail: kmatsus5@jhmi.edu

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

4. **Rationale**:
   Varicose veins are part of the spectrum of lower extremity chronic venous disease and generally more common in older adults and women. In the US, approximately 23% of adults have varicose veins, and estimated 22 million women and 11 million men between the ages of 40 to 80 years have varicose veins.\(^1\) Recently, systemic impact of varicose veins attracts attention of health care providers. For example, varicose veins alone are known to reduce quality of life due
to leg tiredness. In addition, a recent Taiwanese study demonstrated strong association of varicose veins with incident venous thrombosis. Indeed, varicose veins can induce inflammation and thrombotic process (these conditions may predate varicose veins and construct vicious cycle).

However, data on the contribution of varicose veins to subsequent risk of other major cardiovascular diseases such as coronary heart disease and heart failure are limited and inconsistent. A prospective study from Finland observed that those with varicose veins had a higher risk of arterial disease (angina pectoris, myocardial infarction, peripheral artery disease, or cerebrovascular disease) and heart failure than those without. A French prospective study also reported an increased risk of coronary heart disease in patients with varicose veins. In contrast, the Framingham Heart Study reported no association between varicose veins and risk of coronary heart disease once controlling for body mass index and systolic blood pressure. Moreover, in the Normative Aging study, participants with varicose veins had a lower risk of coronary heart disease than those without after adjusting for cardiovascular risk factors. However, these previous studies had some important caveats: selected population (e.g., veterans or police officer), short-term follow-up, and self-reported cardiovascular outcomes.

Therefore, we will comprehensively examine the association of varicose veins with adverse cardiovascular outcomes including mortality and incidence of coronary heart disease, heart failure, stroke and peripheral artery disease (PAD) in the Atherosclerosis Risk in communities (ARIC) Study.

5. Main Hypothesis/Study Questions:
- Varicose veins will be associated with the risk of cardiovascular disease, independently of cardiovascular risk factors (e.g., diabetes, hypertension and smoking status)

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 varicose veins with subsequent cardiovascular disease.

Inclusions:
- All ARIC participants with data on covariates of interest at visit 5 will be included in the analyses

Exclusions:
- Ethnicity other than black and white
- Missing data on covariates of interest at visit 5

Exposures: Clinically recognized varicose veins
- We will capture all ARIC participants who developed clinically recognized varicose veins after visit 1 through visit 5.
- Varicose veins will be defined by hospitalization due to varicose veins or outpatient visits for varicose veins (at least two visits for varicose veins).
Hospitalization due to varicose veins will be identified from ARIC hospitalization data and CMS Medicare data (ICD-9 codes: 454.xx).

Outpatient visits for varicose veins will be identified from CMS Medicare data (ICD-9 codes: 454.xx)

Outcomes:

- The outcome of interest will be all-cause mortality, cardiovascular mortality, coronary heart disease, heart failure, stroke and PAD. Participants will be followed from visit 5 through the end of follow-up (December 31, 2016), date of outcomes of interest including death, or loss to follow-up whichever came first.
- Cardiovascular mortality will be defined as death from coronary heart disease, heart failure, or stroke. Coronary heart disease and stroke will be defined as definite or probable cases adjudicated by ARIC physician panel. Heart failure will be defined as a hospitalization having in any position an ICD-9 code 428 or ICD-10 code I50 for heart failure diagnosis. PAD will be identified based on hospitalizations with the ICD-9 codes (440.2x, 440.3x or 440.4, 39.25, 39.29, or 39.50).

Covariates: socio-demographic characteristics (age, race, gender, education), alcohol intake, smoking status, body mass index, history of cardiovascular disease (coronary heart disease, stroke heart failure, or PAD), hypertension (systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90mmHg, or use of antihypertensive medication), diabetes (fasting blood glucose ≥126mg/dL, non-fasting glucose ≥200mg/dL, reported history of diabetes, or use of anti-diabetes medication), lipid parameters (Total cholesterol, HDL cholesterol and LDL cholesterol), antidysslipidemia medications, ankle brachial index (ABI), and Medicare advantage plan (from CMS Medicare data) at visit 5.

Statistical Analysis:

1. We will summarize baseline characteristics by absence and presence of varicose veins.
2. Cumulative incidence of the outcome of interest will be estimated by absence and presence of varicose veins using the Kaplan-Meier method.
3. We will quantify the association of varicose veins with mortality and incidence of cardiovascular disease using Cox proportional hazards models accounting for potential confounders. We will adjust for demographic variables (age, gender, race, and education levels), body mass index, hypertension, diabetes, total cholesterol, HDL-cholesterol, antidysslipidemia medications, history of cardiovascular disease, smoking status, alcohol intake and ABI (the lowest values of both legs).
4. We will conduct a few sensitivity analyses
   - To assess the association of varicose veins with first development of coronary heart disease, heart failure, stroke, and PAD we will repeat the analysis after excluding each of prevalent cases (e.g., prevalent coronary heart disease at visit 5 will be excluded in the analysis for incident coronary heart disease).
   - To compare the contributions of varicose veins to cardiovascular outcomes in subgroups, we will perform subgroup analysis according to age, gender, race, hypertension, diabetes, history of cardiovascular disease, smoking status and insurance status (e.g., Medicare advantage plan).
Since we cannot capture outpatient visits for varicose veins outside of Medicare fee-for-service beneficiaries aged ≥65 years, we will restrict to ARIC participants enrolled continuously in Medicare Parts A and B through a fee-for-service plan within 2 years prior to visit 5 and repeat analysis.

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 ___ X 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 _____ 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://www2.cscc.unc.edu/aric/approved-ancillary-studies

__ 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)?

#3506: Ankle-brachial index and short-term risk of cardiovascular events in older adults

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _____ Yes _____ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.cscic.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