ARIC Manuscript Proposal #3550

PC Reviewed: 1/14/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Clinical predictors of incident varicose veins in older adults

b. Abbreviated Title (Length 26 characters): Clinical determinants of varicose veins in older adults

2. Writing Group:

Writing group members: Yejin Mok, Shoshana H. Ballew, Anna Kucharska-Newton, Kenneth Butler, Peter Henke, Pamela Lutsey, Maya Salameh, Ron Hoogeveen, Christie M. Ballantyne, Elizabeth Selvin, 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]**

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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 diseases and affect approximately 33 million adults in the United States.[1] Recent studies showed that varicose veins are associated with serious adverse health outcomes such as leg ulceration[2] and deep vein

thrombosis.[3-5] In addition, associations of varicose veins with incidence of peripheral artery disease and other vascular diseases have been reported.[3, 6-9]

Although there are a few established risk factors of varicose veins such as older age, female sex, height, obesity, pregnancy, and a family history of varicose veins,[10-20] some other factors like physical activity,[15, 19-23] smoking,[15, 16, 20-23] and hypertension[18, 20, 24] demonstrated inconsistent results. Of note, previous studies were cross-sectional[12-15, 17-19] or had short-term follow-up (a median follow-up <5 years).[10, 22] Also, most investigated selected populations of whites[10, 12, 15-18, 20-23] or middle-aged individuals[10, 13, 15, 21-24].

Therefore, we will investigate both established, debated, and other potential risk factors and their associations with varicose veins in a bi-racial community-based cohort study. Such an investigation may help identify individuals at high risk and inform the prevention of varicose veins.

5. Main Hypothesis/Study Questions:

- Established risk factors such as age, female sex, obesity, and height will be associated with increased risk of varicose veins.
- Some of other debated and potential risk factors (e.g., lower physical activity) also will be associated with the risk of varicose veins.

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

- To be able to use Centers for Medicare and Medicaid Services (CMS) data to capture outpatient visits for varicose veins as the outcome, we will restructure the ARIC cohort study to determine baseline and build a nested cohort of older individuals.
- We will include all ARIC participants aged 65-70 years at any of five visits (1987-1989, 1990-1992, 1993-1995, 1996-1998 and 2011-2013) or Carotid MRI visit (2004-2006). We will consider first relevant visit date at which participants reached age 65-70 years as baseline.
- Participants will be followed from the baseline through the end of follow-up (December 31, 2015; the last date of CMS data currently available), date of outcome of interest, or loss to follow-up, whichever came first.

Inclusions:

- Participants with data on predictors and covariates of interest at baseline in a nested cohort of older individuals will be included in the analyses

Exclusions:

- Ethnicity other than black and white
- Participants with prevalent varicose veins at baseline
- Missing data on predictors or covariates of interest at baseline

Exposures:

- Established risk factors for varicose veins: older age,[8, 12, 14, 16, 18, 19] female,[10, 13, 14, 19, 22] height,[12, 15, 17, 20] obesity (body weight, body mass index)[10, 15, 16, 18, 19]
- Potential risk factors of varicose veins:
    - Race: white vs. black
        - Most studies focused on whites, and data on racial differences is sparse.[14]
    - Socioeconomic status: education, insurance, family income and occupation at middle-age
        - Some studies suggested that low socioeconomic status was associated with varicose veins,[12, 20, 21] but some other studies demonstrated conflicting results.[8, 15, 17, 18]
    - Cardiovascular risk factors: hypertension, diabetes, dyslipidemia, kidney measures (estimated glomerular filtration rate, albuminuria)
        - The associations of hypertension and diabetes with varicose veins are still debated due to conflicting results.[8, 10, 13, 18, 20, 24] In addition, the association of kidney measures with varicose vein has not been explored.
        - Some previous clinical trials showed that statin therapy reduced the risk of venous thromboembolism.[25, 26] However, the influence of dyslipidemia on venous disease remained unclear.
    - History of cardiovascular disease (coronary heart disease, stroke, peripheral artery disease and heart failure) and cardiac biomarkers: high-sensitive cardiac troponin T (hs-cTnT) and N-terminal-proB-type natriuretic peptide (NT-proBNP)
        - A study suggested a genetic overlap between venous and arterial cardiovascular disease.[27]
        - Heart failure may be associated with the risk of varicose veins through elevated venous pressure.[28]
        - Similarly, hs-cTnT and NT-proBNP, cardiac markers of cardiac damage and overload, respectively, might be associated with the risk of varicose veins.
    - Inflammatory markers: high-sensitive c-reactive protein (hs-CRP) and galectin-3
        - Several studies suggested some inflammatory markers were associated with venous thromboembolism,[29, 30] which is clinically significant complications of varicose veins. Thus, some inflammatory markers, hs-CRP and galectin 3, might be associated with the risk of varicose veins.
    - Lifestyle factors: smoking (current vs. former vs. non, pack-year of smoking), alcohol intake (yes vs. no; alcohol amount [g/day]) and physical activity (ideal vs. intermediate vs. poor by AHA guidelines, intensity of activity [MET-min/week])
        - The association of smoking with varicose veins is still debated.[8, 10, 13, 15-18, 20-23]
        - No consistent association of physical activity with the risk of varicose veins have been shown[10, 13, 16, 17, 19, 20] although exercise is recommended in patients with venous disease.[2]
        - Some studies evaluated the association of alcohol intake with varicose veins, but results are not consistent.[8, 17, 22]

Outcomes: Clinically recognized varicose veins

- We will capture those who developed clinically recognized varicose veins from visit 1 through December 31, 2015.
- Varicose veins will be defined by ICD-9 codes 454.xx and ICD-10 codes I83.xx at any inpatient and outpatient encounters based on ARIC hospitalization data and CMS Medicare data. For outpatient cases at least two encounters with varicose veins diagnosis will be required to reduce the misclassification of overdiagnosis.

Statistical Analysis:

1. We will summarize baseline characteristics by incident varicose veins vs. no incident varicose veins.
2. Cumulative incidence of varicose veins will be estimated by sex and race using the Kaplan-Meier method.
3. We will include each established and potential risk factor in demographically adjusted (age, gender, and race) Cox regression models. Then, we will run multivariable Cox regression models with all risk factors showing significant association with varicose veins in demographically adjusted models.
4. Since we cannot capture outpatient visits for varicose veins outside of Medicare fee-for-service beneficiaries, we will restrict our analysis to ARIC participants enrolled in Medicare Parts A and B through a fee-for-service (i.e., we will exclude ARIC participants who are not enrolled and censor when participants leave Medicare Parts A and B).

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://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

__ **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.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.

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