1.a. Full Title: Ankle-brachial index and long-term risk of fractures: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): ABI and fractures

2. Writing Group:
   Writing group members: Shoshana H. Ballew, Yingying Sang, Andrea L.C. Schneider, Morgan Grams, Laura R. Loehr, Hirofumi Tanaka, Gerardo Heiss, Elizabeth Selvin, Josef Coresh, Kunihiro Matsushita, others welcome.

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

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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).

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3. Timeline: Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale: Lower extremity peripheral artery disease (PAD), commonly defined as ankle-brachial index (ABI) <0.9, affects more than 200 million individuals around the globe.\(^1\) The prevalence increases dramatically with age (from ~1% at age 40-49 to ~15% at age 70-79 years in the US),\(^2\) and the global prevalence increased by 24% from 2000 to
2010.\textsuperscript{1} PAD is associated with an increased risk of mortality as well as cardiovascular events.\textsuperscript{3-5}

PAD also reduces physical function and mobility through limb ischemia,\textsuperscript{6-9} which can induce falls and thus subsequent bone fracture. Additionally, individuals with PAD are reported to have lower bone mineral density.\textsuperscript{10-15} Indeed, some, but not all,\textsuperscript{14} studies have reported the association of PAD with the risk of fracture,\textsuperscript{14-17} with a few caveats. A vast majority of participants in these studies were whites, leaving uncertainty in non-whites. Two out of three positive studies investigated only older men aged $\geq 65$ years,\textsuperscript{14,17} and thus data for women and younger individuals are sparse. Moreover, the other positive study with both genders and wide age range defined PAD based on discharge code for any peripheral atherosclerosis but did not specifically investigate lower extremity PAD based on ABI. Therefore, the aim of the present study is to assess the association of ABI with fracture risk using data from a community-based cohort, the ARIC Study, consisting of middle-aged white and black men and women with follow-up of more than 20 years.

5. Main Hypothesis/Study Questions:
Hypothesis 1: Low ABI will be independently associated with incident hospitalization for fracture, after controlling for other comorbidities such as body mass index, diabetes, hypertension, and history of cardiac disease or stroke.

Hypothesis 2: Some individuals with PAD may manifest high ABI due to vascular calcification. Therefore, we hypothesize that high ABI will be independently associated with incident hospitalization for fracture, after controlling for other comorbidities such as body mass index, diabetes, hypertension, and history of cardiac disease or stroke.

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 population:
All ARIC subjects whose race was identified as either black or white, with data on ABI at visit 1 and non-missing data on covariates of interest.

Exposure (independent variables):
ABI measured at Visit 1 – ABI was calculated as the ratio of ankle systolic blood pressure (SBP) to arm SBP. Ankle SBP is defined as the final ankle SBP measurement out of up to four measurements taken at study Visit 1. Arm SBP is defined as the first arm measurement of SBP, or the second SBP if the first SBP readings are missing. ABI was also assessed at Visits 3 and 4 in subsample, which will be used for sensitivity analysis in this study.

Outcome (dependent variable):
Hospitalizations are assessed via community hospital surveillance and the annual follow-up phone calls, and hospital records are subsequently acquired. Data are currently
available through the year 2011. Primary and secondary ICD9 codes for all discharge diagnoses associated with hospitalization events will be obtained from the hospital record abstraction forms.

As done previously in ARIC, we will initially examine incident hospitalization for fracture due to injury as the outcome (ICD-9 codes 800-829). We will test various definitions of osteoporotic fractures that have been presented in the literature (e.g. femoral neck and vertebral). We will primarily exclude fractures with a code for motor vehicle traffic accidents (ICD-9 code E819. As there is some evidence that fractures due to injury are sometimes coded as pathologic fractures, we will secondarily run analyses including these pathologic fractures (ICD-9 codes 733.1 – 733.19). Although statistical power may be an issue, we will also specifically analyze hip fractures or other fractures in specific sites most related to fall (e.g., upper extremity, vertebral, and pelvic).

Other variables of interest and covariates:
-Sociodemographics: age, race, gender, education level
-Physical information: body mass index, waist circumference, blood pressure, heart rate
-Lifestyle: smoking status, alcohol intake, physical activity
-Comorbidities: diabetes, hypertension, dyslipidemia, kidney function, kidney damage (albuminuria only at visit 4), and history of cardiovascular disease (coronary heart disease, heart failure, and stroke).
-Medications associated with fracture risk (increased fracture risk: antiepileptic, sedatives, anxiolytics, hypnotics, neuroleptics, antidepressants, glucocorticoids; decreased fracture risk: antihypertensives, cholesterol-lowering drugs, hormone replacement therapy).

Statistical Analysis Plan:
We will quantify the fracture burden (cumulative incidence) among ARIC Study participants based on ABI clinical categories subsequently shown. Using Cox proportional hazards models, we will investigate the independent association between ABI and incident fracture hospitalization risk. ABI will be treated as a continuous variable with splines and a categorical variable based on clinical categories (ABI: <0.5, 0.5-0.7, 0.7-0.9, 0.9-1.1, 1.1-1.4 [reference], and ≥1.4) in the models (threshold of 1.3 will be also tested for high ABI instead of 1.4). We will adjust for the covariates listed above, adjusting first for the sociodemographic variables, then adding further adjustment to subsequent models for the physical information and lifestyle variables, medications, and comorbidities. We will repeat the analysis after stratifying the study sample by age, gender, race, and presence/absence of comorbidities such as diabetes, hypertension, obesity, and history of cardiac disease and stroke.

Sensitivity analyses:
We will conduct sensitivity analyses adjusting for incident cardiovascular disease and stroke after baseline as a time-varying covariate. We will also repeat analyses with Visit 3 and 4 ABI measurements as aforementioned.
Limitations:
Our outcome will include only fractures requiring hospitalization. Given that many minor fractures are treated in outpatient setting, our results may not be generalizable to all fractures. However, the association of ABI with severe fractures will have important clinical and public health implications. We may be unable to exclude all fractures due “excessive trauma” or “high trauma”, as some other studies have done in an attempt to better capture osteoporosis-related fractures.\textsuperscript{20} ABI measurement from Visit 1 was measured on a single, randomly selected lower extremity. Lower extremity arterial disease can be unilateral and may not be adequately captured with measurements in one extremity only. However, the effect size of ABI on cardiovascular risk in ARIC is similar to that from other cohorts.\textsuperscript{32} As with any observational study, we will not be able to rule out the possibility of residual confounding. The results may not be generalizable to ethnic groups other than whites and blacks.

7.a. Will the data be used for non-CVD analysis in this manuscript?  \hspace{1cm} ____ Yes  \hspace{1cm} X\hspace{0.5cm} 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?  \hspace{1cm} ____ Yes  \hspace{1cm} ___ 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?  \hspace{1cm} ____ Yes  \hspace{1cm} X\hspace{0.5cm} 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”?  \hspace{1cm} ____ Yes  \hspace{1cm} ___ 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.cscce.unc.edu/ARIC/search.php
\hspace{1cm} ___ X\hspace{0.5cm} Yes  \hspace{1cm} _____ 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)?
There are no proposals investigating the association of ABI and fracture risk. Below are somewhat related proposals:
MP# 1769 - Diabetes, Glycemia, and Incident Fracture Risk: The Atherosclerosis Risk in Communities (ARIC) Study
MP#2245 - Lower extremity arterial disease and cognitive decline: the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study
MP#2312 – Ankle-brachial index and physical function and activity in older individuals: the Atherosclerosis Risk in Communities (ARIC) Study

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.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.
References:


28. McCandless LC. Statin use and fracture risk: can we quantify the healthy-user effect? *Epidemiology.* 2013;24:743-752

