**ARIC Manuscript Proposal #2455**

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| **PC Reviewed: 10/14/14** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Peripheral Artery Disease and Quality of Life in the Community: The Atherosclerosis Risk in Communities Study

**b. Abbreviated Title (Length 26 characters)**: PAD and QOL

**2. Writing Group**:

Writing group members:

Aozhou Wu, BMed, BS; Josef Coresh, MD, PhD, Elizabeth Selvin, PhD, MPH, Hirofumi Tanaka, PhD, Gerardo Heiss, MD, PhD, Alan Hirsch, MD, Bernard Jaar, MD; Kunihiro Matsushita, MD, PhD; others welcome.

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


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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:

Peripheral arterial disease (PAD), commonly identified by an ankle brachial index (ABI) less than 0.9, is common, especially in older adults. In the US, PAD affects over 7 millions individuals (1), including 20% of people aged over 70 years (2, 3). PAD patients have 4-fold higher mortality risk compared with those without PAD (4-6). This is mainly due to higher risk of cardiovascular diseases (CVD), reflecting the property of PAD as a manifestation of systemic atherosclerosis (7).

PAD can also have a substantial impact on patients' quality of life (QOL). As the disease progress, patients may develop claudication and critical limb ischemia (CLI, a condition including limb rest pain, unhealing ulcers or gangrene, and with a rate of amputation reaching up to 25% within one year after diagnosis (8)), resulting in substantial loss of physical functioning, poor QOL (9-14). However most evidence come from small clinical studies (N<~1,000), typically in symptomatic PAD patients recruited from vascular clinics. Prospective investigations of the long-term impact of PAD on QOL and deterioration over time are lacking.

The aim of this study will be to comprehensively investigate the association of PAD-related measures (ABI, leg symptoms by questionnaires, clinical history of PAD during follow-up time, severe disease condition-CLI) with QOL parameters (self-reported health status, physical function/activity, nursing demand, and social status) in a bi-ethnic community-based cohort, the ARIC Study, at and over different stages of life (middle-age and older age) during 25 years of follow-up.

## 5. Study Aim and Main Hypothesis:

PAD measures are independently associated with poor status of QOL

## 6. Design and analysis

***Study design:***

We will use cross-sectional, prospective and case-control designs according to data availability (as summarized in appendix Table on the last page) and study angle summarized below:

- Cross-sectional evaluation of the association between PAD-related measures (ABI, leg symptoms, and history of clinical PAD) and QOL parameters at ARIC visits with key variables of interest (appendix Table 1) (it is likely that visits 1 and 5 with ABI in literally all participants will be primary visits of interest and visits 3 and 4 with ABI in a subsample will be used for secondary analysis).
- Prospective investigation of the contribution of PAD-related measures to subsequent changes in QOL parameters (earlier visits such as visit 1 with long follow-up will be used for primary analysis).
- Given that these two approaches may not capture severe PAD cases like those with critical limb ischemia with 1-year mortality of ~20% (15). To specifically analyze the association of critical limb ischemia with QOL, we will also implement case-control analysis as detailed below.

***Study population:***

*Inclusion criteria:*

White and African-American participants, with key data on PAD-related measures and QOL parameters (appendix Table 1) at visits of interest.

*Exclusion criteria:*

Non-white/non-black participants or those with missing information on key PAD-related measures and QOL parameters at visits of interest.

***Exposure***

- *Ankle brachial index (ABI):* ABI, the ratio of ankle to brachial blood pressure was based on ankle and brachial systolic blood pressures measured with DINAMAP automated oscillometric device at visits 1, 3, and 4 and with OMRON VP-2000 at visit 5.
- *Leg symptom:* Self-reported leg pain at rest or during walk.
- *History of Clinical PAD:* Clinical diagnosis of PAD prior to visits of interest based on self-report and ICD-9 codes: Peripheral vascular disease (443.9); Atherosclerosis of native arteries of the extremities, unspecified (440.20); Intermittent claudication (440.21); Atherosclerosis, extremities, w/ rest pain (440.22); Atherosclerosis of other specified arteries (440.8); Other specified peripheral vascular diseases (I73.8); Peripheral vascular disease, unspecified (I73.9); Amputation (84.1x), Amputation, not otherwise specified (84.91).; Revascularization (38.08, 38.18, 38.38, 38.48, 39.25, 39.29, 39.49, 39.50, 39.56, 39.57, 39.58, 39.90); Atherosclerosis of bypass graft of the extremities (440.3); Lower extremity ulcer (707.1x); Atherosclerosis, extremities, w/ ulceration (440.23); Gangrene (785.4/440.24); Other atherosclerosis of native arteries of the extremities (440.29).

***Covariates***

*Demographics:* age, gender, race, socioeconomics status, and study center
*Physical information:* body mass index (BMI), blood pressure
*Comorbidities:* Hypertension, diabetes, dyslipidemia, coronary heart disease (CHD), heart failure (HF), stroke, and chronic kidney disease (CKD)

***Outcome: QOL parameters*** *(appendix Table 1 in the last page for more details)*

1. Self-reported health status
2. Physical activity assessment (self-reported ability to walk or 4m-walk test without help, self-reported ability to climb stairs without help, and to do chores work around the house)
3. Social status (self-reported work performance, social activity, employee status, and marital status)
4. Mental status (CES depression score, general mental status in life, and medication use for depression)
5. Nursing demand (Needs on someone's help for personal care or stay in nursing house).

***Statistical Analysis Plan:***

We will first cross-sectionally assess the associations of PAD-related parameters (ABI, leg symptoms, and history of clinical PAD) with each component of QOL at relevant visits. The primary analysis will be conducted with data from visits 1 and 5, and sensitivity analysis will be performed with data from visits 3 and 4. As most of these

QOL parameters are coded as binary variables, logistic regression will be mainly used with the adjustment for covariates listed above. Multinomial logistic regression models will be also implemented in some QOL parameters with multiple categories, as appropriate. We will repeat the analysis in several demographic (age, gender and race) and clinical (hypertension, diabetes, dyslipidemia, CHD, and CKD) subgroups.

Subsequently, we will explore the prospective association of PAD-related measures with changes in QOL parameters during follow-up. To maximize follow-up, we will primarily use visit 1 as baseline. The key QOL outcome variables with frequent repeated assessments for this analysis will be self-reported health status, ability to walk without help, marital status, employment status, health problem interfering work or retirement due to health problem, CES depression score, general mental status in life, medication use for depression. Cox proportional hazards and logistic regression models will be used to evaluate the association of PAD-related measures with subsequent QOL, adjusting for covariates listed above. Similar to *Aim 1a*, we will repeat the analysis in various demographic and clinical subgroups.

To specifically evaluate the impact of severe PAD cases (i.e., critical limb ischemia) that may not be necessarily captured in the above cross-sectional and prospective analyses, we will perform age-, gender-, and race-matched case-control investigation, with match ratio of 1: 3, using density-sampling strategy for severe PAD cases and controls. Severe PAD cases will be identified according to hospitalizations with the following ICD-9 codes: Atherosclerosis, extremities, w/ rest pain (440.22); Amputation (84.1x), Amputation, not otherwise specified (84.91); Lower extremity ulcer (707.1x); Atherosclerosis, extremities, w/ ulceration (440.23); Gangrene (785.4/440.24). Controls will be selected using age-, gender-, and race-matched density-sampling strategy. We will test whether QOL parameters summarized above are different between participants with and without severe PAD, using conditional logistic regression models. We will also evaluate whether important comorbidities related to PAD such as diabetes, CKD, and CHD contribute to further decrease in QOL.

***Limitations:***
ABI was only measured in a randomly selected single leg at visit 1. Only a few QOL parameters were assessed uniformly over the follow-up, and thus we will perform several analyses using different time frames. Thus, we may need to summarize our results in a few manuscripts.

**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 ICTDER03 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**

**8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?**
**____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/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)?**
To our knowledge, there are no ARIC proposals specifically focusing on PAD and QOL. As physical activity as a domain of QOL, MP 2312 "Ankle-brachial index and physical function and activity in older individuals" is most relevant. However, key authors of that manuscript contribute to the current proposal and appropriate coordination will be made.

**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/

**12. 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.**

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Appendix:

Table 1: Availability of key exposure and outcome variables through the study

| Year | | 87 88 89 | 90 | 91 92 | 93 | 94 95 | 96 97 98 | 99 | 00 | 01 | 02 03 04 | 05 06 | 07 | 08 09 10 | 11 12 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | Visit 1 | Visit 2 | | Visit 3 | | Visit 4 | | | | | | | | Visit 5 |
| AFU - Form Version | | A | B | C | D | E | F | G | H | I | J | K | L | M | 1 |
| **Exposure** | | | | | | | | | | | | | | | |
| ABI | | | | | | | | | | | | | | | |
| PAD | | | | | | | | | | | | | | | |
| Leg Pain | Leg pain while walk | | | | | | | | | | | | | | |
| | Leg pain stand still | | | | | | | | | | | | | | |
| **Outcome** | | | | | | | | | | | | | | | |
| Self-report health status | | | | | | | | | | | | | | | |
| Physical Function | Able to walk a certain distance(1/4-1/2 miles)without help | | | | | | | | | | | | | | |
| | Able to walk up and down a certain number of stairs without help | | | | | | | | | | | | | | |
| | Able to do chore(heavy) work around house without help | | | | | | | | | | | | | | |
| | Walk with help | | | | | | | | | | | | | | |
| Social Status | Marital status | | | | | | | | | | | | | | |
| | Employ status | | | | | | | | | | | | | | |
| | Social activity impairment | | | | | | | | | | | | | | |
| | Health related work absent | | | | | | | | | | | | | | |
| | Work interfered by pain | | | | | | | | | | | | | | |
| | Retire due to health problem | | | | | | | | | | | | | | |
| Mental Status | Mental status in life (Health Life Profile) | | | | | | | | | | | | | | |
| | CES depression score | | | | | | | | | | | | | | |
| | Medication for depression | | | | | | | | | | | | | | |
| Nursing Demand | Have stayed in nursing house | | | | | | | | | | | | | | |
| | Currently stay in nursing house | | | | | | | | | | | | | | |
| | Need personal care due to health problem | | | | | | | | | | | | | | |