ARIC Manuscript Proposal #3416

PC Reviewed: 6/18/19 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Conventional and non-conventional lipid measures and subsequent risk of lower-extremity peripheral artery disease: The Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:
Writing group members: Minghao Kou, Ning Ding, Shoshana H Ballew, Maya Salameh, Seth Martin, Elizabeth Selvin, Gerardo Heiss, Christie Mitchell Ballantyne, Kunihiro Matsushita, Ron Hoogeveen

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

First author: **Minghao Kou, MHS**
Address:

Phone: Fax:
E-mail:

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, MD, PhD
Address: Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Welch Center for Prevention, Epidemiology, and Clinical Research
2024 E Monument Street, 2-600
Phone: (443) 287-8766
Fax: (410) 367-2384
E-mail: kmatsush@jhsph.edu

3. Timeline:
The analyses will use existing ARIC data, and manuscript preparation will be performed in the following 1 year.

4. Rationale:

Lower-extremity peripheral artery disease (PAD) is estimated to affect more than 200 million adults globally[1]. Persons with PAD have a significantly higher risk of cardiovascular morbidity and mortality than those without [2]. PAD is also associated with adverse lower-extremity outcomes, including intermittent claudication, reduced leg function, and critical limb ischemia (CLI) [3]. In some patients, the first manifestation of PAD can be CLI, a condition leading to either leg amputation or death in half of patients within a year after its diagnosis[4]. Thus, understanding risk factors of PAD is important for early detection and targeted prevention of PAD.

Although the associations of lipid measures (especially conventional ones such as total cholesterol, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and triglyceride) with coronary heart disease and stroke have been extensively studied [5-12], their associations with PAD are actually less understood. For example, total cholesterol, HDL-C and triglyceride are associated with incident PAD in some but not all studies[13]. Furthermore, non-conventional lipid measures such as small-dense LDL-C (sdLDL-C), remnant lipoprotein cholesterol (RLP-C), and LDL-triglyceride (LDL-TG) are found to be predictive of future cardiovascular diseases[14-23], , even in individuals not considered at increased cardiovascular risk based on conventional lipid measures [19, 22]. However, the data for these non-conventional lipid measures and PAD are sparse. A cross-sectional study found that RLP-C levels were elevated among PAD patients with intermittent claudication [24], but a case-cohort study reported that sdLDL-C was not associated with PAD[25]. Furthermore, a recent report from the Women's Health Study suggested that triglyceride-rich lipoproteins may be particularly strongly associated with PAD [26]. However, this finding should be confirmed in men as well as other study settings.

Therefore, we seek to comprehensively assess the relationship of conventional and non-conventional lipid measures with incident PAD using data from ARIC. This biracial community-based cohort will allow us to explore potential gender and racial interactions. Also, based on a large sample size with long follow-up over 20 years, we can uniquely evaluate CLI as an outcome. Understanding these relationships will may help clinicians better identify patients at high risk of PAD and prevent PAD and its subsequent complications.

5. Main Hypothesis/Study Questions:

- Both conventional and non-conventional lipid measures will be associated with incident PAD.
- Of those, triglyceride-related or triglyceride-rich lipid measures (e.g., triglyceride, LDL-TG and RLP-C) will be especially strongly associated with PAD.

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.

Inclusion criteria:
All African American and white participants in the ARIC Study free of prevalent PAD at Visit 4 who have lipid measures.

Exclusion criteria:
- Participants with prevalent PAD at visit 4 (i.e., ABI ≤0.9, self-reported peripheral revascularization, intermittent claudication based on the Rose questionnaire at visit 1 and PAD cases between visits 1 and 4).
- Participants with missing data on lipids, other covariates of interest and incident PAD.
- Participants who identified themselves as non-white/non-black.
- Participants who did not fast for 8 hours

Exposures: Lipid measures
- Conventional lipid measures: Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), estimated low-density lipoprotein cholesterol (LDL-C) by Martin's method[27], triglycerides (TG), non-HDL-C, apolipoprotein A1 (apoA1), and apolipoprotein (apoB).
- Nonconventional lipid measures: Remnant-like particle cholesterol (RLP-C), triglycerides in low-density lipoprotein (LDL-TG), small dense LDL cholesterol (sdLDL-C), and apo E-containing high-density cholesterol (apoE-HDL-C).

Outcome:
Incident clinical PAD, identified based on hospitalization with ICD-9-CM codes based previous literature[28]: atherosclerosis of native arteries of the extremities, unspecified (440.20); atherosclerosis of native arteries of the extremities with intermittent claudication (440.21); atherosclerosis of native arteries of the extremities with rest pain (440.22); atherosclerosis of native arteries of the extremities with ulceration (440.23); atherosclerosis of native arteries of the extremities with gangrene (440.24); other atherosclerosis of native arteries of the extremities (440.29); atherosclerosis of bypass graft of the extremities (440.3); atherosclerosis of other specified arteries (440.8); endarterectomy, lower limb arteries (38.18); aorta-iliac-femoral bypass (39.25); other (peripheral) vascular shunt or bypass (39.25); angioplasty or atherectomy of other non-coronary vessel(s) (39.50).

Among PAD cases, those based on 440.22, 440.23, and 440.24 and those with coexisting codes of leg amputation (84.1x), lower extremity ulcer (707.1x), and gangrene (785.4) will be considered CLI.

We will try to incorporate ICD-10 codes whenever possible.

Covariates:
- Sociodemographic data: age, race, gender, education level
- Physical measurements: body mass index (BMI), systolic and diastolic blood pressure, estimated glomerular filtration rate (eGFR)
- Associated medical comorbidities:
    - Antihypertensive medication use

- Diabetes, defined as fasting glucose level ⩾126 mg/dL (⩾7.0 mmol/L), non-fasting glucose level ⩾200 mg/dL (⩾11.1 mmol/L), self-reported physician diagnosis, or use of antidiabetic medications
- Prevalent coronary heart disease at visit 4 (self-reported clinical history and evidence of prior myocardial infarction by electrocardiogram at visit 1 and adjudicated events between visits 1 and 4).
- Prevalent stroke (self-report at visit 1 and adjudicated events between visits 1 and 4)
- Antihypertensive and antidyslipidemic medications in the past 2 weeks were determined by self-report and inspection of medication bottles brought to the visit.

-Lifestyle factors: smoking status, pack-years of smoking, alcohol status, physical activity (will use data at visit 3), diet

Statistical analysis plan:

-Baseline characteristics will be compared among all participants with quartiles of lipid measures

-Cox proportional hazards models will be used to analyze incident PAD based on different lipid measures as continuous (1-SD) and categorical (quartiles) variables

- Model 1 will be crude.
- Model 2 will be adjusted for demographic variables of age, race, and gender.
- Model 3 will be built on model 2 and further adjusted for BMI, smoking, alcohol use, diet, education level, systolic blood pressure, diabetes, prevalent coronary heart disease, prevalent stroke, antihypertensive drugs and antidyslipidemic medication use.

-We will conduct subgroup analysis by age, gender, race, smoking status, hypertension, diabetes, coronary heart disease, stroke and antihypertensive and antidyslipidemic medication use.

-We will also evaluate the improvement of PAD risk discrimination by adding lipid measures to the base model with non-lipid traditional cardiovascular risk factors (i.e., age, gender, race, blood pressure, antihypertensive medication use, diabetes, and smoking).

-When we test non-conventional lipid measures, we will also explore a base model including conventional lipid measures since non-conventional lipid measures should confer prognostic information beyond conventional lipid measures to have clinical relevance.

-We will comprehensively contrast conventional and non-conventional lipid measures in terms of the strength of associations (hazard ratios per 1SD and quartiles) as well as discrimination improved as done previously [29]

-We will repeat the analysis for CLI as an outcome

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.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)?
The most relevant proposal would be #1832 "A risk prediction model for incident PAD in the ARIC cohort" which includes conventional lipid measures (e.g., total and HDL cholesterols) as candidate predictors. However, this proposal is based on visit 1 variables and does not take into account nonconventional predictors. Also, the lead investigator of #1832, Kunihiro Matsushita, is the senior author of the present proposal and will be in charge of appropriate coordination.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ 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.

Reference

1. Fowkes, F.G.R., et al., *Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis.* The Lancet, 2013. **382**(9901): p. 1329-1340.
2. Criqui, M.H., et al., *Mortality over a Period of 10 Years in Patients with Peripheral Arterial Disease.* New England Journal of Medicine, 1992. **326**(6): p. 381-386.
3. McDermott, M.M., *Lower extremity manifestations of peripheral artery disease: the pathophysiologic and functional implications of leg ischemia.* Circ Res, 2015. **116**(9): p. 1540-50.
4. Norgren, L., et al., *Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II).* J Vasc Surg, 2007. **45 Suppl S**: p. S5-67.
5. Collaboration*, T.E.R.F., *Major Lipids, Apolipoproteins, and Risk of Vascular Disease.* JAMA, 2009. **302**(18): p. 1993-2000.
6. Sharrett, A.R., et al., *Coronary Heart Disease Prediction From Lipoprotein Cholesterol Levels, Triglycerides, Lipoprotein(a), Apolipoproteins A-I and B, and HDL Density Subfractions.* Circulation, 2001. **104**(10): p. 1108-1113.
7. Thompson, A. and J. Danesh, *Associations between apolipoprotein B, apolipoprotein AI, the apolipoprotein B/AI ratio and coronary heart disease: a literature-based meta-analysis of prospective studies.* J Intern Med, 2006. **259**(5): p. 481-92.
8. As, S., et al., *A study of serum apolipoprotein A1, apolipoprotein B and lipid profile in stroke.* J Clin Diagn Res, 2013. **7**(7): p. 1303-6.
9. Castelli, W.P., et al., *Lipids and risk of coronary heart disease The Framingham Study.* Annals of Epidemiology, 1992. **2**(1): p. 23-28.
10. Frost Philip, H., et al., *Serum Lipids and Incidence of Coronary Heart Disease.* Circulation, 1996. **94**(10): p. 2381-2388.
11. Baigent, C., et al., *Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials.* Lancet, 2010. **376**(9753): p. 1670-81.
12. Hindy, G., et al., *Role of Blood Lipids in the Development of Ischemic Stroke and its Subtypes: A Mendelian Randomization Study.* Stroke, 2018. **49**(4): p. 820-827.
13. Criqui, M.H. and V. Aboyans, *Epidemiology of peripheral artery disease.* Circ Res, 2015. **116**(9): p. 1509-26.
14. Joshi, P.H., et al., *Remnant Lipoprotein Cholesterol and Incident Coronary Heart Disease: The Jackson Heart and Framingham Offspring Cohort Studies.* J Am Heart Assoc, 2016. **5**(5).
15. Tada, H., et al., *Remnant lipoproteins and atherosclerotic cardiovascular disease.* Clin Chim Acta, 2019. **490**: p. 1-5.
16. Fujihara, Y., et al., *Remnant Lipoproteins Are Residual Risk Factor for Future Cardiovascular Events in Patients With Stable Coronary Artery Disease and On-Statin Low-Density Lipoprotein Cholesterol Levels <70 mg/dL.* Circ J, 2019.
17. Ivanova, E.A., et al., *Small Dense Low-Density Lipoprotein as Biomarker for Atherosclerotic Diseases.* Oxid Med Cell Longev, 2017. **2017**: p. 1273042.
18. McNamara, J.R., et al., *Remnant-like particle (RLP) cholesterol is an independent cardiovascular disease risk factor in women: results from the Framingham Heart Study.* Atherosclerosis, 2001. **154**(1): p. 229-36.
19. Hoogeveen, R.C., et al., *Small dense low-density lipoprotein-cholesterol concentrations predict risk for coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study.* Arterioscler Thromb Vasc Biol, 2014. **34**(5): p. 1069-77.
20. Sakai, K., et al., *Small dense low-density lipoprotein cholesterol is a promising biomarker for secondary prevention in older men with stable coronary artery disease.* Geriatr Gerontol Int, 2018. **18**(6): p. 965-972.

21. Nishikura, T., et al., *Elevated small dense low-density lipoprotein cholesterol as a predictor for future cardiovascular events in patients with stable coronary artery disease.* J Atheroscler Thromb, 2014. **21**(8): p. 755-67.
22. Saeed, A., et al., *Remnant-Like Particle Cholesterol, Low-Density Lipoprotein Triglycerides, and Incident Cardiovascular Disease.* J Am Coll Cardiol, 2018. **72**(2): p. 156-169.
23. Ding, X.H., et al., *The predictive value of baseline LDL-TG level on major adverse cardiovascular events in a followed up cohort population.* Eur Rev Med Pharmacol Sci, 2017. **21**(5): p. 1060-1064.
24. Wang, T., *Reduction of remnant lipoprotein cholesterol concentrations by cilostazol in patients with intermittent claudication.* Atherosclerosis, 2003. **171**(2): p. 337-342.
25. Duran, K.E., et al. *Abstract 033: Directly Measured Triglyceride-Rich Lipoprotein Cholesterol and Small Dense LDL-Cholesterol Concentrations Associate With Incident Cardiovascular Disease: Prospective Data From the Women's Health Study*. 2019, March 5; Available from: https://www.ahajournals.org/doi/10.1161/circ.139.suppl_1.033.
26. Aday, A.W., et al., *Lipoprotein Particle Profiles, Standard Lipids, and Peripheral Artery Disease Incidence.* Circulation, 2018. **138**(21): p. 2330-2341.
27. Martin, S.S., et al., *Comparison of a Novel Method vs the Friedewald Equation for Estimating Low-Density Lipoprotein Cholesterol Levels From the Standard Lipid ProfileNovel Method vs Friedewald Equation for Estimating LDL-CNovel Method vs Friedewald Equation for Estimating LDL-C.* JAMA, 2013. **310**(19): p. 2061-2068.
28. Matsushita, K., et al., *High-sensitivity cardiac troponin and natriuretic peptide with risk of lower-extremity peripheral artery disease: the Atherosclerosis Risk in Communities (ARIC) Study*. Eur Heart J, 2018. **39**(25): p. 2412-2419.
29. Folsom, A.R., et al., *Prediction of coronary heart disease in middle-aged adults with diabetes.* Diabetes Care, 2003. **26**(10): p. 2777-84.