PC Reviewed: _8_/21_/07   Status: _A___   Priority: 2___
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: PCSK9 variants and PAD

  b. Abbreviated Title (Length 26 characters): PCSK9 variants and PAD

2.   Writing Group:
    Writing group members: Aaron Folsom, Jim Peacock, Vijay Nambi, Eric Boerwinkle

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

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3.   Timeline: paper by fall 07

   4.   Rationale: Peripheral artery disease (PAD) is an important manifestation of atherosclerosis and usually is detected clinically via claudication symptoms or asymptomatically via assessment of ABI. Dyslipidemia is a risk factor for PAD, but diabetes and smoking may be more prominent etiologic factors.

ARIC and the Dallas Heart Study recently showed mutations in PCSK9 were associated with substantially reduced LDL cholesterol and CHD incidence (1). This suggests that moderate lifelong reduction in LDL-C kept CHD risk low. Whether PCSK9 variants are associated with PAD was not explored and therefore unknown.

Two mutations contributed to low LDL-C in blacks (142X and 679X) and these were compared with neither mutation. In whites, a single SNP (42L) was examined. We will examine these variants in relation to prevalent and incident PAD in ARIC.

5. Main Hypothesis/Study Questions:

PCSK9 variants associated with lower LDL-C levels are associated with reduced PAD prevalence and incidence in ARIC.

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).

Exclusions: No permission for DNA use. Missing independent and dependent variable data. Prevalent PAD will be excluded for incident PAD analyses.

Dependent variables: Prevalent PAD (ABI <0.9 or Rose claudication). Incident PAD (new onset of ABI <0.9 or hospitalization for PAD); this definition has been used by Top Wattanakit in previous ARIC papers.

Independent variable: PCSK9 mutations, as defined previously (1)

Covariates: should be little confounding by other factors, but will consider main risk factors: race, age, sex, smoking, hypertension, BMI, drinking status, diabetes, etc. Lipids are intervening variables, not confounders.

Analysis: We will re-verify no association between risk factors, other than race and lipids, and PCSK9 variants. We will use logistic regression for analysis of prevalent PAD and proportional hazards for incident PAD. If any association is observed, we will model LDL-C to see if it may contribute to the association as an intervening variable. Generally, we will need to pool men and women, blacks and whites, because of the low frequency of the protective alleles. For the most part, covariates will be modeled as baseline variables, though we will consider a supplemental analysis using time dependent covariates for incident PAD. Another supplemental analysis will explore differences in ABI distribution by genotype.

Refs
1. Cohen JC et al. NEJM 2005;354:1264-72.

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 ICTDER02 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 ICTDER02 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?   ___x_ 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 ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
        __x__ 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

    ____xx__ 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)?

   ARIC   1093   Sequence variations in PCSK9, low LDL, and protection against coronary heart disease

   ARIC   997   Risk factors for peripheral arterial disease incidence in persons with diabetes: the Atherosclerosis Risk on 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/

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.**