ARIC Manuscript Proposal # 3065

PC Reviewed: 11/14/2017 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Association of Monocyte Myeloperoxidase and CVD

b. Abbreviated Title (Length 26 characters): **Monocyte MPO and CVD**

2. Writing Group: Aaron Folsom, Abayomi Oyenuga, David Couper, Eric Boerwinkle, others invited

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _____ **[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).

Name:
Address:

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3. Timeline: complete by spring 2018

4. Rationale:

Myeloperoxidase (MPO) is a member of the heme peroxidase superfamily. It constitutes about 5% of human neutrophil protein and catalyzes the conversion of hydrogen peroxide (H2O2) to hypochlorous acid (HOCl). Upon activation, neutrophils secrete large quantities of MPO which produces HOCl that reacts with plasma constituents such as various lipoprotein particles and

endothelial cells to promote atherosclerosis and other forms of vascular diseases. Several prospective studies suggested that plasma MPO is positively associated with incident CHD (1-3). The ARIC carotid MRI study in 2005-6 measured monocyte MPO (mMPO), not plasma MPO, using flow cytometry. A previous publication found mMPO to be inversely associated with prevalent PAD (4). Adjusted for conventional risk factors, the odds ratio for PAD for the highest vs lowest tertile of mMPO was 0.45 (p = .002). The authors attributed this somewhat unexpected inverse relation between mMPO content and PAD to release and depletion of mMPO during monocyte activation in PAD patients. Also in the carotid MRI study, mMPO was inversely associated with carotid wall volume on MRI, though not with cap thickness or lipid core of the main identified carotid plaque (5). Other studies of mMPO or leukocyte MPO have also shown inverse associations with CVD (5,6).

With 10 years of follow-up since the carotid MRI study, we now should be able to study the association of mMPO with incident CVD. A limitation of this research is that we do not know the within person repeatability of mMPO.

5. Main Hypothesis/Study Questions:

Is mMPO associated with incident CVD (CHD, stroke, heart failure, PAD, CVD mortality)?

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).

Design: cohort beginning at carotid MRI exam (n=2066) in 2005-6
Inclusion: whites and Af Ams who attended carotid MRI exam and had the main independent variables measured
Exclusions: prevalent CVD
Main exposure: mMPO measured by flow cytometry
Outcome: time to incident CVD (pooled CHD, heart failure, stroke, PAD, CVD mortality)
Other variables: age, race, sex, major CVD risk factors.

Analysis:
Analyses will use sampling weights to adjust for the Carotid MRI sampling design. We will examine the interrelations of MPO with covariables. We will explore the shape of the relation of MPO with CVD using cubic splines, and use an appropriate form in Cox regression.

We will run a series of models. Model 1 will adjust for demographics. Model 2 will further adjust for major CVD risk factors. If incident CVD N's allow, we will also look at CHD, HF, stroke, and PAD as separate outcomes.

References

1. Meuwese, M.C., et al., Serum myeloperoxidase levels are associated with the future risk of coronary artery disease in apparently healthy individuals: the EPIC-Norfolk Prospective Population Study. J Am Coll Cardiol, 2007. **50**(2): p. 159-65.

2. Wong, N.D., et al., Myeloperoxidase, Subclinical Atherosclerosis, and Cardiovascular Disease Events. JACC: Cardiovascular Imaging, 2009. **2**(9): p. 1093-1099.

3. Karakas, M., et al., Myeloperoxidase is associated with incident coronary heart disease independently of traditional risk factors: results from the MONICA/KORA Augsburg study. J Intern Med, 2012. **271**(1): p. 43-50.

4. Matijevic, N., et al., The ARIC Carotid MRI Study of Blood Cellular Markers: An Inverse Association of Monocyte Myeloperoxidase Content With Peripheral Arterial Disease. Angiology, 2011. **62**(3): p. 237-244

5. Matijevic N, Wu KK, Howard AG, Wasserman B, Wang WY, **Folsom AR**, Sharrett AR.Association of blood monocyte and platelet markers with carotid artery characteristics: the atherosclerosis risk in communities carotid MRI study. Cerebrovasc Dis. 2011;31(6):552-8. PMID: 21487219

6. Biasucci, L.M., et al., Intracellular neutrophil myeloperoxidase is reduced in unstable angina and acute myocardial infarction, but its reduction is not related to ischemia. J Am Coll Cardiol, 1996. **27**(3): p. 611-6.

7. Buffon , A., et al., Widespread Coronary Inflammation in Unstable Angina. New England Journal of Medicine, 2002. **347**(1): p. 5-12.

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/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)?

1205 or 1207 Matijevic N, Wu KK, Nidkarni N, Heiss G, Folsom AR. The ARIC carotid MRI study of blood cellular markers: an inverse association of monocyte myeloperoxidase content with peripheral arterial disease. Angiology. 2011 Apr;62(3):237-44. PMID: 21406422

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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __x__ No.