ARIC Manuscript Proposal # 1128

PC Reviewed: _01/24/06   **Status:** _____   **Priority:** _____
SC Reviewed: _____   **Status:** _____   **Priority:** _____

1.a. Full Title: Relationship between carotid artery stiffness and age-related macular degeneration

b. Abbreviated Title (Length 26 characters): Carotid Artery Stiffness and AMD

2. Writing Group:

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Writing group members: Cheung N, Duanping Liao, Ronald Klein

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]

3. Timeline:

The intent of this analysis is to investigate the cross-sectional association of the age-related macular degeneration and carotid artery stiffness. Initial analyses and writing will take place between Jan and May 2006, and final writing and manuscript submission between June 2006 and October 2006.

4. Rationale:

Several studies have linked age-related macular degeneration (AMD) with structural [1] [2, 3], functional [2-4] and biochemical [5-11] markers of atherosclerosis, though the findings are not universally consistent [12].

The Rotterdam Eye Study in the Netherlands found increased risk of prevalent late AMD and incident early or late AMD in persons with carotid artery atherosclerosis [2]. Plaques in the carotid bifurcation (odds ratio 4.7; 95% confidence interval, 1.8 to 12.2) and common carotid artery (OR 2.5; 95%CI, 1.4 to 4.5) were shown to associate with increased risk of AMD. After more than 5 years of follow-up, in addition to carotid plaques, increased carotid wall thickness was also found to increase risk of AMD (OR 1.15; 95%CI, 1.03 to 1.28), even after extensive adjustments for confounders [3]. Furthermore, the Atherosclerosis Risk in Communities (ARIC) Study in 1999 also reported an independent association of carotid plaque with retinal pigment epithelial depigmentation (OR 1.77; 95%CI, 1.18-2.65), nevertheless, referring to the large

number of associations studied, it was concluded that atherosclerosis was unrelated to ARM overall [1].

Functional measure of atherosclerosis by ankle-brachial index has also been reported to associate with AMD. The Rotterdam Eye Study demonstrated a statistically significant 2.5 times increased prevalence odds of late AMD in persons with ABI less than 0.9 [2]. This, however, could not be confirmed by the recent Beaver Dam Eye study [13], in which, despite higher proportions of participants with early and late AMD were found to be associated with low ABI (22.1% with early AMD vs 18.8% without, 5.3% with late AMD vs 1.7% without), the associations were not statistically significant. This negative finding was suggested to be due to the small number of cases of late AMD in the study population [13].

Lastly, biomarkers of atherosclerosis, too, have been linked to AMD. A recent case-control study of 156 persons (79 with AMD) from the AMD Genetic Study Group found that individuals with AMD have higher serum levels of homocysteine and C-reactive protein (CRP), both of which have been found to associate with carotid artery atherosclerosis [11].

In light of the conflicting evidence of an association between AMD and carotid artery atherosclerosis, we postulate that AMD may be associated with carotid artery stiffness, an early manifestation of atherosclerosis that has been shown to increase risk of ischemic stroke and cardiovascular mortality.

5. Main Hypothesis/Study Questions:

1. Is carotid artery stiffness associated AMD in the ARIC study?
2. If so, is this related to a particular AMD lesion (drusen, pigmentary change etc)?
3. If so, is the association independent of age, gender, race, cigarette smoking, hypertension and other cardiovascular risk factors?

6. Data (variables, time window, source, inclusions/exclusions):

(1) AMD variables. Any AMD, early AMD, late AMD and specific AMD lesions (drusen, pigmentary changes)
(2) Carotid artery stiffness (derived from systolic carotid arterial diameter, diastolic carotid arterial diameter, and the change in carotid arterial diameter between systole and diastole, concurrent brachial blood pressure (BP) measured every 30 seconds, and the average of 2 BP measures during ultrasound examination). Carotid arterial elasticity, as BP-adjusted arterial diameter change (AADC), include average diastolic arterial diameter, average systolic arterial diameter, average diameter change, diastolic BP, systolic BP, and pulse pressure.
(3) Covariates: age, sex, ethnicity, education levels, cigarette smoking, alcohol consumption, body mass index, fasting serum total cholesterol, triglycerides, high-density lipoprotein and low-density lipoprotein cholesterols, diabetes mellitus, blood pressure, hemostatic and inflammatory markers (von Willebrand factor, factor VIIIc, fibrinogen, WBC)
(4) Exclusion criteria: From participants at ARIC visit 3 (n=12,887), exclude persons who whose race is not black/white, with ungradeable retinal photographs or missing retinal variables for AMD and carotid artery stiffness parameters at visit 3.

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 ICTDER01 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 ICTDER01 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 ICTDER01 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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.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)?
- Klein R, Clegg L, Cooper LS, et al. Prevalence of age-related maculopathy in the Atherosclerosis Risk in Communities Study. Arch Ophthalmol 1999;117:1203-10.

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. primiarly 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.

References

1.   Klein, R., et al., *Prevalence of age-related maculopathy in the Atherosclerosis Risk in Communities Study.* Arch Ophthalmol, 1999. **117**(9): p. 1203-10.
2.   Vingerling, J.R., et al., *Age-related macular degeneration is associated with atherosclerosis. The Rotterdam Study.* Am J Epidemiol, 1995. **142**(4): p. 404-9.
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4. Zheng, Z.J., et al., *Associations of ankle-brachial index with clinical coronary heart disease, stroke and preclinical carotid and popliteal atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study.* Atherosclerosis, 1997. **131**(1): p. 115-25.

5. Bang, O.Y., et al., *Inflammatory markers, rather than conventional risk factors, are different between carotid and MCA atherosclerosis.* J Neurol Neurosurg Psychiatry, 2005. **76**(8): p. 1128-34.

6. Benbir, G., M. Bozluolcay, and B. Ince, *Is the level of C-reactive protein correlated with the extent of carotid atherosclerosis?* Acta Neurol Belg, 2005. **105**(2): p. 73-80.

7. Durga, J., et al., *Homocysteine and carotid intima-media thickness: a critical appraisal of the evidence.* Atherosclerosis, 2004. **176**(1): p. 1-19.

8. Gonzalez-Gay, M.A., et al., *High-grade C-reactive protein elevation correlates with accelerated atherogenesis in patients with rheumatoid arthritis.* J Rheumatol, 2005. **32**(7): p. 1219-23.

9. Samson, R.H., Z. Yungst, and D.P. Showalter, *Homocysteine, a risk factor for carotid atherosclerosis, is not a risk factor for early recurrent carotid stenosis following carotid endarterectomy.* Vasc Endovascular Surg, 2004. **38**(4): p. 345-8.

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11. Vine, A.K., et al., *Biomarkers of cardiovascular disease as risk factors for age-related macular degeneration.* Ophthalmology, 2005. **112**(12): p. 2076-80.

12. Klein, R., et al., *Early age-related maculopathy in the cardiovascular health study.* Ophthalmology, 2003. **110**(1): p. 25-33.

13. Moss SE, K.R., Klein BEK, *Ankle-brachial index and the prevalence of age-realted maculopathy.* Am J Ophthalmol, 2005. **140**: p. 1159-61.