ARIC Manuscript Proposal # 1234

PC Reviewed: _3_/13_/07	**Status: __A__**	**Priority: _2__**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: 10-year Incidence, Progression and Regression of Retinal Vascular Abnormalities and their Relationship with Vascular and Inflammatory Risk Markers.

b. Abbreviated Title (Length 26 characters): 10-year Incidence of Retinal Signs

2. Writing Group:

Writing group members: F Amirul Islam, Gerald Liew, Ronald Klein, Barbara EK Klein, A Richey Sharrett, Mary Frances Cotch, Jie Jin Wang

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

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3. Timeline:

The intent of this analysis is to prospectively investigate the 10-year incidence, progression and regression of focal retinal vascular lesions (focal arteriolar narrowing, arterio-venous nicking, and retinopathy) as well as changes in retinal vessel calibers, and their relationship to baseline vascular and inflammatory factors. We will use baseline

data from ARIC Visit 3 (1993-95) and 10-year incident retinal outcomes from Visit 5 (2004-5). Initial analyses and writing will take place between June and September 2007, and final writing and manuscript submission between August and November 2007

4. Rationale:

Retinal Vascular Abnormalities are related to Cardiovascular Disease

The retina is a unique site where the structure of the microcirculation can be imaged directly. Retinal photography was first performed at ARIC Visit 3 (1993-95), for which we developed reproducible and accurate methods for measuring retinal vascular parameters.[1] Using these methods, we showed that in the ARIC population retinal vascular parameters such as small arteriole-to-venule ratio (AVR, a measure of arteriolar narrowing relative to venules or venular widening relative to arterioles), focal arteriolar narrowing, arterio-venous nicking and retinopathy lesions are strongly related to hypertension, with arterio-venous nicking additionally related to markers of inflammation and endothelial dysfunction.[2] In the same population, we demonstrated that several retinal vascular parameters predicted the onset of important systemic diseases. Small AVR and focal arteriolar narrowing predicted 60% higher risk of incident hypertension, while arterio-venous nicking and retinopathy lesions as well as small AVR were independent predictors of risk of stroke.[3] Small AVR also predicted risk of coronary heart disease in women, but not in men.[4] Similar findings have been reported from other populations in Europe and Australia,[5-10] suggesting that analysis of retinal vascular parameters may be useful adjuncts to cardiovascular risk prediction.[11]

The Incidence, Progression, and Regression of Retinal Vascular Abnormalities are Unclear.

Our understanding of the systemic correlates and clinical significance of retinal vascular parameters has improved substantially in the last few years, but several important questions remain unanswered. Firstly, there are few data on the natural history of retinal vascular abnormalities. In the Beaver Dam Eye Study (US), about 6-10% of people developed incident focal vascular lesions (focal arteriolar narrowing, arterio-venous nicking, and retinopathy) over a 5-year period.[12] In the Blue Mountains Eye Study (Australia), 10% of an older population without diabetes developed incident retinopathy after 5 years, while 72% of baseline retinopathy lesions regressed.[13] In the ARIC study, we have recently analyzed data on 1,000 people who had retinal photography at Visit 3 and Visit 4. We reported that the 3-year incidence (cumulative prevalence) of any retinopathy in the whole cohort was 3.8% (7.7%) but this seemed perhaps unreasonably high for just a 3 year period, given that overall prevalence at baseline was about 7%. In multivariable analysis, incident retinopathy was related to higher mean arterial blood pressure (OR 1.5, 95% CI 1.0, 2.3, per standard deviation increase in risk factor levels), fasting serum glucose (OR 1.6, 95% CI, 1.3, 2.1), serum total cholesterol (OR 1.4, 95% CI, 1.0, 2.0), and plasma fibrinogen (OR 1.4, 95% CI, 1.1, 1.9). The 3 year incidence (cumulative prevalence) of retinopathy among persons without diabetes was 2.9% (4.3%). Incident retinopathy in non-diabetic persons was related to higher mean arterial blood pressure (OR 1.4, 95% CI, 0.9, 2.3) and fasting serum glucose (OR 1.5, 95% CI, 1.0, 2.3). Of the 70 people with any retinopathy signs at the 3rd examination, 40 (57.1%) had persistent retinopathy signs at the 4th examination, but 30

(42.9%) did not have retinopathy signs in the same eye at the 4th examination. After controlling for age, gender, race and center, these 30 persons with "apparent regression" of retinopathy were less likely to have diabetes, were never/past cigarette smokers, and had smaller waist hip ratios, higher levels of physical activity, and lower levels of fasting glucose and factor VIII. Longer term changes are unclear and we will now be able to determine the 10-year incidence and regression of these retinal vascular signs between Visit 3 and Visit 5

Secondly, except for evidence from cross-sectional associations with age, it is not known how retinal vessel calibers change over time. Variations in retinal arteriolar and venular calibers have been found in the ARIC study and other populations to convey prognostic information on the risk of stroke and coronary heart disease,[6,10] but longitudinal changes in retinal vessel calibers have not been studied in detail. Thus it is not known to what extent narrowing of vessels occurs with aging, and what systemic factors are associated with these changes.

Thirdly, the long-term impact of cardiovascular risk factors (e.g. hypertension, diabetes, smoking, dyslipidemia, high body mass index), subclinical measures of atherosclerosis (e.g. carotid intima-media thickening (IMT) and plaque, popliteal artery thickening, carotid arterial stiffness) and inflammatory states on the evolution of vascular abnormalities (e.g., retinopathy, A/V nicking and focal narrowing) and changes in vessel calibers over time is not known. Our group has previously reported that subclinical measures of large artery atherosclerosis are not associated with prevalent retinal vascular abnormalities or retinal vessel calibers,[2] except for an association of carotid plaque with small AVR.[2] Inflammatory markers are also associated with prevalent arterio-venous nicking and wider venular calibers.[14-16] These studies reported only cross-sectional associations - the prospective effects of cardiovascular risk factors, subclinical atherosclerosis and markers of inflammation on changes in retinal vascular structure remain unknown.

The ARIC study rephotographed 2000 selected participants 10 years after initial retinal photography. This provides an ideal opportunity to prospectively study 10-year incidence, progression and regression of retinal vascular abnormalities, and longitudinal changes in retinal vessel caliber. This proposal also aims to examine the impact of baseline vascular and inflammatory factors on these 10-year changes.

Clinical significance of proposal

This proposal will describe the natural history of retinal vascular abnormalities and longitudinal change in retinal vessel calibers. The data obtained will (1) improve understanding of the temporal evolution of retinal vascular signs and parameters, and (2) assist in determining the clinical utility of retinal photography in cardiovascular risk prediction.

This proposal will also determine the long-term effects of cardiovascular risk factors, subclincal measures of atherosclerosis, inflammatory markers and genetic factors on structural changes in the retinal microcirculation. Such data are sparse due to difficulties in noninvasively imaging the microcirculation, and may provide insights into the pathophysiology of vascular disease.

5. Main Hypothesis/Study Questions:

(1) To quantitatively describe the incidence, progression and regression of retinal vascular abnormalities over 10 years.
(2) To describe longitudinal changes in retinal vessel calibers over 10 years.
(3) To investigate the association of vascular and inflammatory factors on the incidence, progression and regression of retinal vascular abnormalities and on longitudinal changes in retinal vessel calibers.

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).

Analytic Strategy

We will define incidence of retinal signs as the appearance of retinal signs at visit 5 in persons without these signs at visit 3; progression as an increase in severity of signs (e.g. from mild to severe AV nicking); and regression as disappearance of these signs between visit 3 and 5. We will use logistic regression to examine the relationship of incidence, progression and regression of signs with factors such as age, sex, baseline blood pressure, diabetes, carotid IMT and plaque and other relevant variables as described earlier. A similar strategy will be applied for change in vessel calibers between visit 3 and 5.

Exclusions

Not in Visit 3
Race not Black or White
Black residents in Minneapolis and Maryland
No retinal photographs

Data variables (time of collection)

(1) Retinal vascular variables at baseline (visit 3): Retinopathy, focal arteriolar narrowing, arterio-venous nicking, central retinal arteriolar equivalent, central retinal venular equivalent.
(2) Retinal vascular variables at 10 year follow-up (visit 5): Retinopathy, focal arteriolar narrowing, arterio-venous nicking, central retinal arteriolar equivalent, central retinal venular equivalent.
(3) Baseline cardiovascular risk factors (visit 3): systolic blood pressure (visits 1, 2, 3), diastolic blood pressure (visits 1, 2, 3), hypertension, antihypertensive medication use, diabetes, fasting plasma glucose, diabetic medication use, duration of diabetes, cigarette smoking status (never, past, current), pack-years of smoking, plasma total cholesterol, HDL cholesterol, triglycerides, cholesterol lowering medications, body mass index, waist to hip ratio.
(4) Baseline measures of atherosclerosis (visit 3): carotid IMT and plaque, popliteal artery thickening, carotid arterial stiffness.

(5) Baseline inflammatory and endothelial function biomarkers (visit 3): fibrinogen, white blood cell count, von Willebrand factor, factor VIII (last two variables from visit 1).
(6) Covariates: age, race, center, education, income, occupation, physical activity, prevalent coronary heart disease and stroke, alcohol consumption.
(7) Variables to correct measurement error (visit 3): the repeat measurements of retinal vascular variables, particularly arteriolar and venular diameters, central retinal arteriolar equivalent, central retinal venular equivalent, arteriole-to-venule ratio from the Individual Variability Study (n = 206), and the Grader Variability Study (n = 495) as described by Couper et al.[17]

Possible Limitations

The main limitation is the nonrandom nature of the sample that was rephotographed at ARIC visit 5. The sample was selected to obtain 60% of baseline participants with high carotid IMT (>85 percentile), with the remaining 40% randomly sampled from the remaining population (<85 percentile). However, we have previously shown carotid IMT is not associated with the retinal vascular parameters we are studying,[2] suggesting that selection on carotid IMT should not bias our sample with regards to the outcome (incidence of retinal vascular abnormalities and changes in retinal vessel calibers). We will perform analyses stratified by carotid IMT category, and perform weighted analysis, adjusting for sampling fractions. We will consult closely with the Coordinating Center on this, as the sampling fractions are not straightforward. We will acknowledge this potential bias in our Discussion, and be conservative in our interpretation of the findings.

Another potential limitation is statistical uncertainly in analyzing longitudinal change in retinal vessel calibers, which were measured with error at both time points. To address this methodological issue, we plan to analyze change in vessel calibers in two ways (1) without additionally adjusting for baseline measures, as this may introduce bias, and (2) using the method of moments to obtain measurement error corrected estimates. These methods have been shown to provide less biased estimates of the predictors of longitudinal change in continuous variables such as carotid IMT.[18]

Unpublished data from other studies (e.g. Blue Mountains Eye Study, JJW) indicate that some focal retinal signs 'disappear' over time. This may represent a true phenomenon, with resolution/regression of signs, or may represent misclassification of signs. To guard against misclassification, we plan to perform 'side by side' grading of visit 3 and visit 5 retinal photographs with signs, with a panel of retinal specialists to adjudicate disappearance of lesions between visit 3 and 5.

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? ____ 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 ICTDER02 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)? Not relevant.

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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