

ARIC Manuscript Proposal # 1424

PC Reviewed: 09/09/08
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Systematic review of the association between retinal microvascular signs and cardiovascular disease

b. Abbreviated Title (Length 26 characters):

CVD and retinal signs – a systematic review

2. Writing Group:

Writing group members:

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

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3. Timeline:

Several studies have reported on the association between retinal microvascular signs and cardiovascular disease. These results have been inconsistent. The purpose of this study is to investigate the differences between the results reported. We have conducted a systematic search of the literature and have identified the ARIC study as one of the studies that has recorded retinal microvascular signs and cardiovascular outcomes. The principal investigators of the Blue Mountains Eye Study, Beaver Dam Eye Study, AusDiab and Rotterdam study have agreed to provide their data for this study. Initial analyses and writing will take place between September 2008 and December 2008, and final writing and manuscript submission between January 2009 and March 2009.

4. Rationale:

Recently, a number of large epidemiological studies have reported associations between retinal microvascular signs and incident cardiovascular outcomes such as stroke and coronary heart disease (CHD).¹⁻¹⁰ Wider retinal venules, narrower arteriolar calibre and retinopathy lesions have been independently linked with increased risk of CHD and stroke in several populations, but uncertainties remain regarding the consistency of associations, the magnitude of effect, and the subgroups in which these effects are manifest most strongly. These questions are important and relevant to efforts to explore the use of retinal photography in cardiovascular risk prediction.

The Blue Mountain Eye Study (BMES) reported that retinopathy was associated with stroke⁵ although this result was not found in the Cardiovascular Health Study (CHS)⁷. Arteriolar caliber has been shown to be associated with coronary heart disease in the CHS population⁷, but only amongst women in the BMES and ARIC^{6,10}. Other retinal microvascular signs have been investigated in some studies and not others. Venular caliber has been shown to be associated with stroke in the CHS population and the Rotterdam study^{4,7} but this has yet to be investigated in ARIC.

Specific aims

A meta-analysis is proposed that will combine the individual participant data from ARIC and the other studies that have been identified from a systematic literature search. The primary objectives of this analysis are

- To describe the age and sex-specific associations between retinal microvascular signs and incident cardiovascular disease;
- To determine whether these associations are independent of the risk factors in the Framingham risk score and other traditional and non-traditional cardiovascular risk factors;
- To determine whether the retinal microvascular signs add to the predictive ability of current CVD risk prediction methods such as the Framingham risk score;

- To explore the possible sources of heterogeneity between studies including study and participant level characteristics.

Literature search

The electronic databases Medline and Embase have been searched for studies that meet the following criteria (1) cohort studies that have used retinal photography to record the presence of microvascular retinal signs and/or the diameters of retinal calibers at baseline, (2) have at least one year of follow-up available, (3) data available on cause specific CVD morbidity and/or mortality outcomes.

Table 1 lists the studies that have been identified from the literature search and that will be approached to contribute the individual participant data to be included in the meta-analysis.

Table 1: Studies that have recorded retinal signs and cardiovascular outcomes

Study	Sample Size
Atherosclerosis Risk in Communities Study ¹⁰	12887
Cardiovascular Health Study ¹¹	1992
Blue Mountains Eye Study ⁶	3654
Beaver Dam Eye Study ⁹	4926
Rotterdam Study ¹²	5540
AusDiab ¹³	2177

These studies listed are all community based cohort studies that have recorded retinal calibers. A number of other studies that have been carried out amongst specific populations (eg people with diabetes or hypertension) or amongst general population but which have not recorded retinal calibers have also been identified. However, the focus of this analysis will be on the investigation of the association between retinal arteriolar and venular calibers and CVD in a general population.

The quality of studies that match the selection criteria will be assessed using the guidelines published in by Hayden et al.¹⁴ These guidelines recommend assessing the following aspects of each study - study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, analysis – to determine the risk of bias. The heterogeneity of results between studies of different quality will then be examined.

5. Main Hypothesis/Study Questions:

1. What are the age and sex-specific associations between retinal arteriolar and venular calibers and incident cardiovascular disease?;
2. Are these associations are independent of the risk factors in the Framingham risk score and other traditional and non-traditional cardiovascular risk factors?;

3. Do the retinal arteriolar and venular calibers add to the predictive ability of current CVD risk prediction methods such as the Framingham risk score?;
4. What study and participant level characteristics are associated with the differences in effect measures between studies?

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).

1. Study design: Meta analysis of individual participant data
2. Inclusion criteria: Participants attending third visit
3. Exclusion criteria: 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 variable at visit 3, and prevalent CHD and stroke at baseline or prior to visit 3.
4. Outcomes: Incident CHD and incident stroke within 10 years of visit 3.
5. Study factor: Retinal arteriolar and venular caliber. The raw vessel calibers are requested as well as the summary measures central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE). This will allow the retinal calibers to be summarized using the Knudtson as well as the Parr-Hubbard formulas.
6. Covariates: age, sex, race, center, prevalent MI, CHD, or CVD, diabetes and hypertension status, blood pressure, lipids (total cholesterol, LDL-C, HDL-C, TG), hemostatic and inflammatory markers (von Willebrand factor, factor VIIIc, fibrinogen, WBC), cigarette smoking, alcohol consumption, body mass index (variables from ARIC visit 1-3, except for von Willebrand factor, factor VIIIc, WBC, fibrinogen available ARIC visit 1 only). Where appropriate, adjustment will be made for covariates averaged over ARIC visit 1-3 (e.g., 6-year averaged blood pressure, 6-year averaged glucose, 6- year averaged BMI, etc). Additional measurements of these variables recorded before, during or after visit 3 are also requested to adjust for regression dilution.
7. Data analysis: Cox proportional hazards models will be used to estimate the association between the microvascular retinal signs and CVD outcomes. The estimated hazard ratios will be adjusted for the traditional and non-traditional CVD risk factors. Hierarchical models will be used to explore heterogeneity and combine the individual patient data in the meta-analysis.^{15, 16} Adjustment for regression dilution will be carried out for studies that have repeat measurements available for the study factors and/or covariates.¹⁷

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 ICTDER03 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.csc.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)? ARIC MS# 1110, "Risk Prediction of Coronary Heart Disease based on Retinal Vascular Caliber: The Atherosclerosis Risk in Communities 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.csc.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

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15. Bennett DA. Review of analytical methods for prospective cohort studies using time to event data: single studies and implications for meta-analysis. *Stat Methods Med Res* 2003;12:297-319.
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