

**ARIC Manuscript Proposal # 1110r**

**PC Reviewed:**   4  /  10/07  

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**Priority:**           

**1.a. Full Title:** Risk Prediction of Coronary Heart Disease and Stroke using Retinal Arteriolar and Venular Signs.

**b. Abbreviated Title (Length 26 characters):** CVD Prediction using Retinal Vascular Signs

**2. Writing Group:**

**Writing group members:**

McGeechan K, Liew G, Macaskill P, Irwig L, Wang JJ, Klein R, Klein B, Sharrett AR, Chambless LE, Wong TY.

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

Kevin McGeechan

**[please confirm with your initials electronically or in writing]**

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### **3. Timeline:**

The intent of this analysis is to evaluate the incremental value of retinal arteriolar and venular calibers and vascular signs (focal signs – focal narrowing, arterio-venous nicking, retinopathy lesions) in the prediction of incident coronary heart disease (CHD) and stroke events in addition to that already predicted by traditional cardiovascular risk factors. Initial analyses and writing will take place between June 2007 and October 2007, and final writing and manuscript submission between October 2007 and December 2007.

### **4. Rationale:**

In the past few years, data from a number of population-based studies have shown that retinal vascular signs are associated with an increased risk of incident CHD and stroke events, even after adjustment for traditional risk factors.<sup>1</sup> However, there remain two important gaps in the literature.

#### **Association of CVD with Retinal Arteriolar and Venular Caliber**

In our initial analysis of the ARIC study, we had reported associations between smaller retinal arteriole-venular ratio (AVR), an indicator of relative caliber of arterioles to venules, and 3-year incident stroke and CHD, while controlling for blood pressure and other risk factors.<sup>2,3</sup> These associations were initially thought to reflect the association between retinal arteriolar narrowing and the incident cardiovascular diseases, based largely on earlier analyses that showed increasing levels of blood pressure were associated with narrower arteriolar caliber, but had no effect on venular caliber.<sup>4,5</sup> We also found an interaction of AVR and incident CHD with gender, with stronger associations in women than men, suggesting that microvascular disease may be more prominent in women.

New studies, however, now suggest that this interpretation may be incorrect. The AVR may represent either smaller retinal arteriolar caliber or larger venular caliber. These studies show that larger retinal venular caliber is associated with a range of cardiovascular risk factors, including diabetes, obesity and biomarkers of inflammation.<sup>6-8</sup> In the Rotterdam study,<sup>6</sup> the Beaver Dam Eye Study,<sup>7</sup> and the Multi-Ethnic Study of Atherosclerosis (MESA),<sup>8</sup> larger venular caliber was associated with C-reactive protein and interleukin-6, independent of age, blood pressure and other factors.

In the Cardiovascular Health Study, larger retinal venular caliber was associated with both 5-year incident CHD and incident stroke.<sup>9</sup> The Rotterdam Study reported an association of wider venular caliber with 8.5-year incident stroke events.<sup>10</sup> Analysis of data from the Blue Mountains Eye Study has shown an association between larger venular calibers and 9-year mortality from CHD.<sup>11</sup> This analysis also found an association between smaller arteriole calibers and CHD mortality amongst women, but not men.

With these new findings, it is important to re-visit the ARIC data to examine whether retinal arteriolar or venular caliber is associated with incident CHD and stroke. The new analysis will be compared to our previous findings, including possible interaction with gender.<sup>2</sup> We also take the opportunity to examine associations of different cardiovascular risk factors with retinal arteriolar and venular caliber separately, comparing our results to earlier work.<sup>7,8</sup>

#### **Risk Prediction using Retinal Vascular Caliber**

Current methods for estimating the risk of a cardiovascular event include combining risk factors in a risk prediction equation to obtain a summary 5 or 10-year predicted absolute risk, which may then be used to determine treatment options for patients.<sup>12</sup> Many novel risk factors have been proposed that hold promise for improving the predictive ability of current risk

prediction models. However, recent studies have demonstrated that an association of elevated CVD risk with a novel risk factor often does not translate into an improvement in the prediction of CVD events.<sup>13,14</sup> For example, using data from the ARIC study, Chambless et. al. analysed 11 nontraditional risk factors (including body mass index, fibrinogen etc) together with traditional risk factors and found that the combination substantially improved risk prediction of future CHD events in men and to a lesser extent in women. The same authors conducted a similar analysis with incident stroke events, and reported that addition of nontraditional risk factors did not improve risk prediction for stroke sufficiently to warrant inclusion in clinical practice.<sup>15</sup> Hence there is a need to go beyond association studies and examine if novel risk factors will contribute meaningfully to clinical risk prediction.<sup>16</sup>

The proposed paper will determine whether the elevated risks associated with larger venules and smaller arterioles, as well as focal signs, leads to improvements in prediction of CHD and stroke. We will also examine whether the use of retinal calibers and focal signs in risk prediction equations would alter the predicted risk by such an extent that the recommended treatment may change.

Thus, this proposal will allow us to address 2 related issues

1. Associations of Retinal Arteriolar and Venular Caliber. In the ARIC study, we had previously published that narrower AVR is associated with incident CVD events. However, subsequent studies have shown that both arteriolar and venular calibers convey prognostic information on CVD risk – hence this proposal provides the opportunity to examine in closer detail the specific relationships of arteriolar and venular calibers with CVD outcomes. We will also examine associations of different cardiovascular risk factors with retinal arteriolar and venular caliber separately, comparing our results to earlier work. This part of our proposal has been approved in a previous ARIC proposal (#1110r, “Retinal Arteriolar and Venular Caliber and Incident Cardiovascular Disease”) on 3 Jan 2006, and we would like to combine that proposal with this current one.
2. Risk Prediction using Retinal Caliber Measurements. We will now further examine the ability of retinal vascular caliber measurements to add to prediction of CHD and stroke. In this analysis, we will also incorporate repeatability estimates in retinal vessel calibers for both short term (same visit) and longer term (between visit 3 and visit 5). We will thus be able to address issues of the degree of variability and measurement error in the retinal vascular measurements, and how they influence the predictive ability of retinal variables. Several members of the writing group (K McGeechan, L Irwig, P Macaskill) have research interests in measurement error<sup>17,18</sup> and will liaise with the ARIC Coordinating Centre to incorporate these measures (as suggested in the letter by the ARIC P&P recommendations dated 3 Jan 2006).

## **5. Main Hypothesis/Study Questions:**

1. Is smaller arteriolar caliber or larger retinal venular caliber associated with 10-year incident CHD and stroke in the ARIC study (separate analyses for CHD and stroke)? If so, are these associations independent of age, gender, race, cigarette smoking, hypertension and other cardiovascular risk factors? Are the associations different in men and women?
2. Do retinal arteriolar and venular calibers improve the prediction of incident stroke and CHD above that already predicted by traditional risk factors? If so, is the predictive value of retinal calibers different for men and women for CHD and stroke, and for people with and without diabetes?

3. What is the short and long term variability of retinal vessel measurements, and how does this variability impact on their predictive value?
4. How do different traditional (e.g., hypertension, smoking, diabetes, dyslipidemia) and novel (e.g., white blood cell count, fibrinogen, carotid IMT) cardiovascular risk factors relate to retinal vascular signs?

**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: Cohort study
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 (CRAE, CRVE) and the focal retinal signs (retinopathy, microaneurysms, retinal hemorrhages, soft exudates), focal narrowing and arterio-venous nicking
6. Covariates: age, sex, race, center, prevalent CHD and MI, 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).
7. Data analysis:
  - a. Associations with 10-year incident CHD, and stroke. All analyses will be performed for CHD and stroke separately, and in men and women separately, in line with the separate published Framingham risk prediction models for CHD and stroke used in clinical guidelines. Unadjusted hazard ratios will be calculated for each of the study factors using Cox regression. Hazard ratios will then be calculated adjusted for traditional and non-traditional CHD risk factors.
  - b. Predictive value of retinal vascular signs for CHD and stroke. The incremental gain in CHD (and stroke) prediction will be measured using the change in the area under the ROC curve. We will test for improved ROC score using nested models: one with all variables (including the entire batch of retinal variables of interest) vs. another model without any retinal variables. A SAS macro for comparing time-dependent area under the ROC is available to test for improvement in risk prediction.<sup>19</sup> In addition to ROC score enhancement, we will examine the number of participants who move from one risk category to another (e.g. from <10% 10-year risk in 10 years to >10% 10-year risk) when retinal variables are added, as well as the number who drop out of, or enter into, 'meriting treatment' categories. We can display this graphically with a plot of CHD risk by risk deciles in two models: one with all variables except retinal variables and the other model also including the retinal variables. If the latter is better, the risk level pertaining to the top deciles will be higher, and the risk level pertaining to the bottom deciles will be lower. This will help demonstrate the clinical utility of retinal vascular signs. We will perform analyses in men and women separately, and in those

with and without diabetes, as per our apriori hypotheses that retinal vessel caliber will be more informative in women,<sup>2</sup> and in persons with diabetes.

- c. Impact of variability in retinal vessel measurements on risk prediction. We will use the repeat measurements of the retinal signs taken at visits 4 and 5 to estimate the short and long term variability in retinal sign measurements, particularly retinal vessel caliber. Using these estimates, we will adjust for measurement error and determine how this impacts on risk prediction. We will utilize methods we have previously developed,<sup>17,18</sup> and liaise closely with the coordinating center to determine appropriate analytical approaches.
- d. Relationship of traditional and novel cardiovascular risk factors with retinal vessel caliber. We will use logistic and linear regression models to estimate the change in arteriolar and venular calibers with change in levels of traditional and novel risk factors such as blood pressure, white cell count, carotid IMT, following the approach of earlier studies.<sup>7,8</sup>

**7.a. Will the data be used for non-CVD analysis in this manuscript?**    ☐ Yes    ☒ 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    ☒ 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/csc/ARIC/stdy/studymem.html>  
☒ 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)?**

1. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and incident coronary heart disease in women and men: The Atherosclerosis Risk in the Communities Study. JAMA 2002; 287:1153-9.
2. Wong TY, Klein R, Couper DJ, et al Retinal microvascular abnormalities and incident strokes. The Atherosclerosis Risk in the Communities Study. Lancet 2001; 358: 1134-40.
3. Chambless LR, Folsom AR, Sharrett AR et al Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. J Clin Epidemiol 2003; 56:880-890.

**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

1. Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med*. 2004;351:2310-2317.
2. Wong TY, Klein R, Sharrett AR et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. *JAMA*. 2002;287:1153-1159.
3. Wong TY, Klein R, Couper DJ et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. *Lancet*. 2001;358:1134-1140.
4. Wong TY, Hubbard LD, Klein R et al. Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. *Br J Ophthalmol*. 2002;86:1007-1013.
5. Sharrett AR, Hubbard LD, Cooper LS et al. Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 1999;150:263-270.
6. Ikram MK, de Jong FJ, Vingerling JR et al. Are retinal arteriolar or venular diameters associated with markers for cardiovascular disorders? The Rotterdam Study. *Invest Ophthalmol Vis Sci*. 2004;45:2129-2134.
7. Klein R, Klein BE, Knudtson MD, Wong TY, Tsai MY. Are inflammatory factors related to retinal vessel caliber? The Beaver Dam Eye Study. *Arch Ophthalmol*. 2006;124:87-94.
8. Wong TY, Islam FM, Klein R et al. Retinal vascular caliber, cardiovascular risk factors, and inflammation: the multi-ethnic study of atherosclerosis (MESA). *Invest Ophthalmol Vis Sci*. 2006;47:2341-2350.
9. Wong TY, Kamineni A, Klein R et al. Quantitative retinal venular caliber and risk of cardiovascular disease in older persons: the cardiovascular health study. *Arch Intern Med*. 2006;166:2388-2394.
10. Ikram MK, de Jong FJ, Bos MJ et al. Retinal vessel diameters and risk of stroke: the Rotterdam Study. *Neurology*. 2006;66:1339-1343.
11. Wang JJ, Liew G, Wong TY et al. Retinal vascular caliber and the risk of coronary heart disease-related mortality. *Heart*. 2006.
12. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
13. Chambless LE, Folsom AR, Sharrett AR et al. Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. *J Clin Epidemiol*. 2003;56:880-890.
14. Folsom AR, Chambless LE, Ballantyne CM et al. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the atherosclerosis risk in communities study. *Arch Intern Med*. 2006;166:1368-1373.
15. Chambless LE, Heiss G, Shahar E, Earp MJ, Toole J. Prediction of ischemic stroke risk in the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 2004;160:259-269.
16. Ware JH. The limitations of risk factors as prognostic tools. *N Engl J Med*. 2006;355:2615-2617.
17. Chan SF, Macaskill P, Irwig L, Walter SD. Adjustment for baseline measurement error in randomized controlled trials induces bias. *Control Clin Trials*. 2004;25:408-416.
18. Turner MJ, Irwig L, Bune AJ, Kam PC, Baker AB. Lack of sphygmomanometer calibration causes over- and under-detection of hypertension: a computer simulation study. *J Hypertens*. 2006;24:1931-1938.
19. Chambless LE, Diao G. Estimation of time-dependent area under the ROC curve for long-term risk prediction. - *Stat Med*. 2005;2005 Oct 11;.