ARIC Manuscript Proposal #2604

PC Reviewed: 9/8/15   **Status: <u>A</u>**   **Priority: <u>2</u>**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title:

1. Systematic review and individual participant meta-analysis of the association between retinal vessel caliber and Chronic Kidney Disease.
2. Systematic review and individual participant meta-analysis of the association between retinal vessel caliber and Diabetic Kidney Disease.

b. Abbreviated Title (Length 26 characters):

1. Retinal vessel caliber and CKD.
2. Retinal vessel caliber and DKD.

2. Writing Group:
Writing group members:

Sabanayagam C, McKay GJ, Patterson CC, McGowan A, Beatty M, Klein R, Klein B, Mitchell P, Wong TY, Xie J, Broe R, Grauslund J, others from different cohorts, Maxwell AP.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. <u>CS</u>

First author: Charumathi Sabanayagam
     Address: Singapore Eye Research Institute
                     The Academia, 20 College Road, Discovery Tower Level 6
                     Singapore, 169856
     Phone: Tel: +65 6576 7286 / Fax: +65 6225 2568
     Email: charumathi.sabanayagam@seri.com.sg

Corresponding/senior author (must be an ARIC investigator for the proposal but can be different in the published paper; correspondence will be sent to both the first author & the corresponding author): Tien Y Wong, MD, PhD
     Address: Singapore Eye Research Institute
                     Singapore National Eye Centre
                  11 Third Hospital Avenue
                     Singapore 168751
     Phone: Tel: +65 63224571 / Fax: +65 63231903
     Email: tien_yin_wong@nuhs.edu.sg

3. Timeline:
1 year. Several prospective studies have reported an association between retinal microvascular signs and risk for kidney disease, including renal complications associated with diabetes. We wish to obtain more precise values for the magnitude of this association and effect size between retinal vascular caliber separately for both chronic kidney disease (CKD) and diabetic kidney

disease (DKD), and to evaluate the additional predictive value of these measures, through undertaking a meta-analysis based on all published data. Previously, we have performed two such meta-analyses in which we focused on stroke[1] and coronary heart disease[2]. We are now extending this project and propose to perform the following two meta-analyses:

1. Retinal vascular caliber and the risk for CKD.
2. Retinal vascular caliber and the risk for DKD.

We have conducted a systematic search of the literature and have identified the ARIC study as one of the studies which have extensive data on caliber measurements, incident outcomes (renal function, diabetes) and data on additional confounders. The principal investigators of the Blue Mountains Eye Study, Beaver Dam Eye Study, AusDiab, the Multi-Ethnic Study of Atherosclerosis, Rotterdam study and other studies have agreed to provide their raw individual level data for this study. Initial analyses and writing will take place between August 2015 and November 2015, and final writing and manuscript submission between December 2015 and July 2016.

4.   Rationale:
Over the last 10 years several large population-based studies have examined the role of the microcirculation in the development of cardiovascular diseases. This has been done by using a semi-automated system to quantitatively assess retinal vascular caliber. The focus has been on several cardiovascular diseases including stroke, heart diseases, hypertension and diabetes mellitus. With respect to hypertension, there has been a remarkable consistency across individual studies showing that retinal arteriolar narrowing increases hypertension risk. In contrast, the association of retinal vessel caliber with kidney disease (both CKD and DKD), are inconsistent. Furthermore, uncertainties remain regarding the additional value of retinal vascular caliber measurements above that of the traditional risk factors in the prediction of these diseases.

Specific aims
Two meta-analyses are 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 the analyses are:
- To explore potential differences in the association between retinal vessel caliber and CKD and DKD separately by age, sex and ethnicity in a cross-sectional analysis.
- To explore associations of retinal vessel caliber with incident CKD or DKD in datasets that have longitudinal data available
- To determine whether the associations are independent of other traditional and non-traditional risk factors
- To determine the extent to which risk scores improve on addition of retinal vessel caliber to the predictive ability of current CKD and DKD risk prediction methods
- To explore the possible sources of heterogeneity between studies including study and participant level characteristics

Literature search
Study selection & data extraction
Criteria for study inclusion predicates participant level measures of renal function, retinal vascular caliber from either 35 mm photographic film or digital photographs using computer-assisted methods at a single time point. The primary outcome measure will be based on a cross-sectional analysis of case control data. Where prospective data is available, a secondary analysis will investigate individual level data between 2 time points (4-5 years apart) to evaluate the

association of retinal vascular caliber with incident CKD or DKD. Incident CKD will be defined as eGFR < 60 mL/min/1.73m^2 at a 4-5 year follow-up in combination with those individuals who experience a decrease in eGFR from baseline to follow-up ≥25% in participants who had eGFR ≥ 60 mL/min/1.73m^2 at baseline (i.e. those with eGFR < 60 mL/min/1.73m^2 at baseline will be excluded) as defined by Grams and colleagues. [3]

To minimize potential confounding from diabetes, a nested analysis will be performed where individuals with a confirmed diagnosis of diabetes will be excluded from the CKD analysis. Only individuals with diabetes will be included in the DKD analysis. Where albuminuria data is available, a nested analysis will be undertaken on those with an eGFR<60 mL/min/1.73m^2 and the presence or absence albuminuria.

A literature search was conducted of MEDLINE and EMBASE. Reference lists and conference proceedings were also searched to identify possible additional studies. The following search terms were used: (microvessel.mp. or microvascular.tw., vessel.mp. or vascular.tw., arteriole.mp. or arteriolar.tw., venule.mp. or venular.tw.) and (kidney disease). Further studies and unpublished data were sought by discussion between collaborators. Possible studies for inclusion were independently assessed for suitability by three authors (CS, AMG, and GMK) and any lack of clarity or disagreement was resolved by discussion.

The quality of studies that match the selection criteria will be assessed using the guidelines published by Hayden et al.[4] These guidelines recommend assessing the following aspects of each study - study participation, study attrition, measurement of prognostic factor, outcome, confounding factors, and analysis – to determine the risk of bias. The heterogeneity of results between studies of different quality will then be examined. **Table 1** lists the studies identified from the literature search that fulfil the inclusion criteria and have agreed to contribute data to be included in the meta-analysis.

Table 1: Sample size of included studies

Study	Sample Size (n=36,309)
Atherosclerosis Risk in Communities Study (ARIC)[5]	7899
The Australian Diabetes, Obesity and Lifestyle (AusDiab)[6]	768
Beaver Dam Eye Study (BDES)[7]	3135
Blue Mountains Eye Study (BMES)[8]	2971
Multi-ethnic Study of Atherosclerosis (MESA)[9]	4955
Singapore Malay Eye Study (SiMES)[10]	2915
Singapore Prospective 2 Program (SP2)[11]	3602
Cardiovascular Health Study (CHS)[12]	1394
Rotterdam Study (RS)[13]	4927
Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)[14]	2014
Renin-angiotensin System Study (RASS)[15]	234
Danish Cohort of Pediatric Diabetes 1987 (DCPD1987)[16]	185
Type 1 diabetic patients from Fyn County, Denmark (T1DFCD)[17]	188
Irish Nun Eye Study[18]	1122

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

   1. What are the age, ethnicity and sex-specific associations between retinal arteriolar and venular caliber and CKD and DKD?

2. Do we observe similar associations in both cross-sectional and longitudinal analyses on incident kidney disease?
3. Are these associations independent of other traditional and non-traditional risk factors?
4. Do the retinal arteriolar and venular caliber add to the predictive ability of current CKD and DKD risk prediction?
5. What study and participant level characteristics are associated with the differences in effect measures between studies?

Paper 1 - CKD
Primary outcome measure: Association of retinal vascular caliber with CKD with a nested analysis of those participants with diabetes excluded.
Secondary outcome measure: Association of retinal vascular caliber with incident CKD.

Paper 2 - DKD
Primary outcome measure: Association of retinal vascular caliber with DKD.
Secondary outcome measure: Association of retinal vascular caliber with incident DKD with a sub-analysis which has defined DKD as an eGFR<60 mL/min/1.73m^2 and the presence of albuminuria.

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).**

Inclusion criteria: Study participants with eGFR (to determine CKD status), presence/absence of diabetes, retinal arteriolar /venular caliber

The following retinal microvascular variables will be sought from the study investigators:

1) Arteriolar and venular caliber (raw vessel caliber data as well as summary measures);
2) CKD or DKD status.

In order to adjust for traditional and non-traditional risk factors, and to determine whether the retinal microvascular variables add to the predictive ability of current risk prediction methods the following covariates will also be sought (where available):

<u>Socio-demographic characteristics</u>
Age, sex, race, socio-economic status, education level

<u>Blood pressure</u>
Systolic BP, diastolic BP, history of hypertension, anti-hypertensive medication use and type (ARB/ACE inhibitors/calcium channel blockers)

<u>Blood glucose</u>
HbA1c, use of anti-diabetic medication, presence and type of diabetes, duration of diabetes

<u>Blood lipids</u>
Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, cholesterol lowering medication use

<u>Lifestyle factors</u>

Weight, height, waist and hip circumference, cigarette smoking, alcohol consumption, physical activity, use of exogenous hormones

Renal function
Serum creatinine, eGFR, albuminuria/proteinuria, albumin creatinine ratio
C-reactive protein

Analysis Plan

Cross-sectional analysis. We will use logistic regression to model the odds of having CKD or DKD. Adoption of a two-stage analysis method as proposed previously,[19] will consider potential study-specific design bias and covariates not uniformly defined or coded across studies, which make both evaluation of a joint model difficult and allow the dependent variable risk (CKD or DKD) to vary between cohorts. Odds ratio estimates will be derived initially with adjustment only for age and gender and subsequently with additional adjustment for confounding variables such as smoking, body mass index and type of diabetes. Interaction terms will be added to the logistic model to assess consistency of retinal vessel caliber findings from cohort to cohort. Should retinal vessel caliber show predictive value we will derive measures of discriminatory ability (C statistics and reclassification indexes) and assess calibration using the Hosmer-Lemeshow deciles of risk approach.[20] The model will initially be derived in the cohorts of predominantly White subjects and will subsequently be applied in Asian cohorts to assess the repeatability and generalizability of findings across populations. To minimise potential confounding from diabetes in the CKD study, a nested analysis will be undertaken where individuals with a confirmed diagnosis of diabetes will be excluded. We are fully aware of the difficulties of employing estimated glomerular filtration rates to measure kidney function.[21] We will calculate the eGFR using the CKD-EPI formula[22] derived from the 4-variable MDRD equation.[23]

Longitudinal analysis. The discrete-time proportional hazards (complementary log-log link) models for interval-censored data for incident CKD/DKD will be used because only the interval during which new CKD/DKD develops is available (i.e. the exact date of onset of DKD between 2 examinations cannot be determined). The estimated hazard ratios (HR) will be adjusted for the traditional and non-traditional risk factors. We will pool the log HR estimates for the different studies by random effects meta-analysis[24] and display outputs in forest plots.

The extent of heterogeneity between studies will be evaluated with the inconsistency I² statistic.[25] Validity of the above two-stage analyses results (with estimates of association calculated separately within each study, followed by pooling of the association estimates from different studies) will be assessed by fitting a one-stage multilevel discrete time (Cox regression) random effect model using pooled individual data of all studies, with a random intercept to account for study-specific effects.

We will perform subgroup analyses using interaction tests to assess statistical evidence of any differences in HR across levels of pre-specified individual level characteristics including age, sex, ethnicity, current smoking, body mass index and hypertension status. We will perform subgroup analyses in DKD stratified by type of diabetes and age group (adults/children). We will also perform the following sensitivity analyses to test the robustness of our results:
First we will perform a leaving one study out approach, calculating the pooled effect of remaining studies and comparing the results with the combined effect based on all the studies. Second, to explore the possibility of reverse causality i.e. CKD/DKD causing retinal microvascular changes,

we will repeat the analysis after excluding those with shorter follow-up of (e.g. 3 years or 5 years).

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes ____ 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? __X__ Yes
   (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.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)? 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   _____ 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 for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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 ____ No.

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