1.a. Full Title: Retinal Arteriolar Caliber and 10-year incidence of Hypertension.

b. Abbreviated Title (Length 26 characters): Retinal caliber and Incident Hypertension

2. Writing Group:
   Writing group members: 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:
   This analysis aims to prospectively test the hypothesis that narrower retinal arteriolar caliber is associated subsequently with 10-year incidence of hypertension, after adjusting for baseline blood pressure and other risk factors. We will use baseline data from ARIC Visit 3 (1993-95) and 10-year incident outcomes from Visit 5 (2004-5). Initial analyses
and writing will take place between July and September 2007, and final writing and
manuscript submission between October and December 2007.

4. **Rationale:**

Hypertension affects 1 billion persons worldwide, and up to 7.1 million deaths a
year may be attributable to hypertension. A distinctive feature of hypertension is
increased peripheral vascular resistance, which is determined largely by narrower
arterioles in the systemic microcirculation. However, one of the central unresolved
issues in hypertension pathophysiology is whether narrower arteriole contributes to the
development of hypertension, or is purely a secondary adaptation to elevated blood
pressure.4

Histologically, narrower arterioles reflect sclerotic changes leading to increased
wall thickness from intima and media hyperplasia and decreased internal lumen, as well
as reactive and transient vasoconstriction. Some of these processes are thought to occur
early, before the onset of established hypertension, and are postulated to increase
peripheral resistance and initiate or amplify other pressor stimuli (e.g. salt retention),
leading to the establishment and maintenance of hypertension (structural amplifier
hypothesis). It has been hypothesized that relatively modest decreases in internal lumen
caliber, particularly in the renal pre-glomerular vasculature, are sufficient to ‘reset’
blood pressure at a higher level by altering hemodynamics in a manner similar to renal
artery stenosis. However, it is difficult to test the hypothesis that arteriolar narrowing
occurs prior to the onset of hypertension, as most methods for examining the human
microcirculation are invasive and do not permit sampling of the same vascular region
more than once.

The retina is a unique site where the microcirculatory vessels can be visualized
directly, allowing detailed analysis of arteriolar structure in vivo. The ARIC study was
one of the first epidemiological studies to quantitatively measure retinal arteriolar caliber
from retinal photographs and examine its relationship with hypertension. In 2004, our
group reported that smaller arteriole-to-venule ratio (AVR, a measure of arteriolar
narrowing relative to venules or venular widening relative to arterioles), as well as
smaller arteriolar caliber (unpublished data) at ARIC visit 3, when retinal photography
was first performed, predicted 60-70% higher risk of developing incident hypertension
after 3 years (ARIC visit 4) independently of other risk factors such as body size, diabetes
and baseline blood pressure. This provided the first prospective clinical evidence showing
that narrower arteriolar caliber preceded the development of clinical hypertension, and
was not purely a secondary response to established hypertension. However, systolic
blood pressure increased by a similar amount in participants with both narrower as well
as wider arteriolar caliber, suggesting that narrower arterioles did not contribute to the
rise in blood pressure. These results though, should viewed with caution given the
relatively short follow-up time period of 3 years, during which misclassification of
hypertension status could have occurred, and the possibility that narrower arterioles may
contribute to greater blood pressure increase over longer time periods. Nonetheless, the
relationship between smaller AVR and incident hypertension has now been confirmed in
3 other population-based studies – the Beaver Dam Eye Study, Blue Mountains Eye
Study and Rotterdam Study. Additionally, the latter two studies have established that
the association resulted from narrower arteriolar, rather than wider venular, caliber.
In 2004-5 (ARIC visit 5), about 2000 selected participants were re-examined again 10 years after the initial retinal photography. This provides an ideal opportunity to prospectively examine the relationship of retinal arteriolar caliber with cumulative 3 and 10 year incident hypertension. It also permits us to determine if narrower retinal arterioles over a longer time period correlate with greater risk of hypertension.

5. Main Hypothesis/Study Questions:
(1) Narrower retinal arteriolar caliber at baseline (visit 3) is associated with cumulative 10-year incident hypertension (visit 5), independent of other factors such as age, gender, race, body size, diabetes, smoking and previous baseline blood pressure.
(2) Persons with narrower retinal arteriolar caliber at baseline (visit 3) experience greater increase in blood pressure over 10 years (visit 5) than persons with wider retinal arteriolar caliber at baseline, independent of other factors (e.g. age, gender, race, body size, diabetes, smoking and previous baseline blood pressure).

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).

Study Design
We will perform discrete linear logistic regression analyses modeling incident hypertension as a time dependent covariate. This method allows persons who developed incident hypertension at either 3-year (visit 4) or 10-year (visit 5) follow up to contribute data to the analyses. Given the strong influence of age on the arteriolar caliber-blood pressure relationship observed in ARIC and other populations, we will test apriori for interaction between age and arteriolar caliber on incident hypertension and future blood pressure and stratify the analyses by age.

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): retinal arteriolar and venular caliber (central retinal arteriolar equivalent, central retinal venular equivalent) and focal lesions (retinopathy, focal arteriolar narrowing, arterio-venous nicking).
(2) Baseline cardiovascular risk factors (visit 3): systolic blood pressure, diastolic blood pressure, 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.
Baseline measures of atherosclerosis, inflammatory and endothelial function biomarkers (visit 3): carotid IMT and plaque, popliteal artery thickening, carotid arterial stiffness, fibrinogen, white blood cell count, von Willebrand factor, factor VIII (last two variables from visit 1).

Important covariate: Hypertension status, systolic, diastolic blood pressure and antihypertensive medication use at visits 1, 2 and 3.

Outcome variable: Hypertension status, systolic, diastolic blood pressure and antihypertensive medication use at 3 years (visit 4) and 10 years (visit 5) follow up.

Demographics and other covariates: age, race, center, education, income, occupation, physical activity, prevalent coronary heart disease and stroke, alcohol consumption

Potential Limitations
There are 2 potential limitations.

1. Non-random ARIC visit 5 sample. 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). In our preliminary analyses of v3 data, we found no association between carotid IMT and retinal arteriolar caliber after adjusting for age, sex, race and center, suggesting that selection on carotid IMT should not bias our sample with regards to the outcome. However, carotid IMT is strongly associated with blood pressures and may thus bias our results. 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 place caveats on the generalisability of our findings.

2. Lack of adequate power. 60% of the 2000 participants re-sampled at visit 5 were selected based on high carotid IMT, suggesting a high likelihood they will have baseline hypertension and hence be excluded from analyses of incident hypertension. In our preliminary analyses using visit 3 data, 56% of participants with high carotid IMT had prevalent hypertension, while 40% of participants with low carotid IMT had prevalent hypertension. Hence we would exclude 0.56*0.6*2000 + 0.4*0.4*2000 = 992 participants, leaving 1008 without hypertension at baseline. A further 10% would be excluded because of ungradable retinal photographs, leaving 900 participants to contribute longitudinal data to the analyses. At $\alpha=0.05$, n=900 and assuming 44% of participants develop hypertension over 10 years (extrapolating from the 14% who developed incident hypertension in the 3 years between visit 3 and visit 4), our proposed analyses would have 80% power to detect a 55% difference in risk between persons with narrower retinal arterioles and those without.

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?  __X__
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)?

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.

References

2003;361:1629-1641.
6. Folkow B. Comments on "endpoints in hypertension": peripheral resistance vessels--though mainly on their involvement as "starting-points". *Blood Press Suppl.* 1997;2:34-38.