

## ARIC Manuscript Proposal #3494

PC Reviewed: 10/8/19  
SC Reviewed: \_\_\_\_\_

Status: \_\_\_\_\_  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Association between midlife hypertension with late-life retinal OCT measures

**b. Abbreviated Title (Length 26 characters):** Midlife HTN and retinal OCT

### 2. Writing Group:

Writing group members:

Xinxing Guo, Pradeep Ramulu, A. Richey Sharrett, Ali Abraham, Lubaina Arsiwala, YaNan Dong, Keenan Walker

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

**First author: Pradeep Ramulu**

Address: 600 N Wolfe Street, Suite Wilmer 129, Baltimore MD 21287

Phone: 410-614-1994

Fax:

E-mail: pramulu@jhmi.edu

**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: **Richey Sharrett**

Address: 615 N Wolfe Street

Room W6011

Baltimore, Maryland 21205

Phone: 443-286-1784

Fax:

E-mail: rsharrett@jhu.edu

### 3. Timeline:

First set of analysis December 2019. First draft Dec2020

### 4. Rationale:

The long-term impact of hypertension on the eye, both with regards to structural and vascular measures, has been well-studied in numerous previous reports. Population-based studies have generally found no associations between hypertension and glaucoma, a common disease defined by structural changes in the optic nerve. However, more recent studies have suggested cross-

sectional associations between hypertension and retinal nerve fiber layer thickness (a measure of optic nerve damage),<sup>1</sup> a higher 10-year incidence of retinal nerve fiber layer (RNFL) defects in patients with baseline hypertension,<sup>2</sup> and also greater longitudinal declines in RNFL thickness over 4 years in persons with hypertension, as compared to those without hypertension. Data also exist suggesting that optic nerve damage is more prevalent with low blood pressure<sup>3</sup> and also when blood pressure is low as a result of anti-hypertensive medications. However, the timeframe of these past studies remains short as compared to the lifetime of the individual, such that impact of blood pressure in mid-life on structural measures of the decades later remains unknown. Likewise, very limited data exist describing the associations of mid-life blood pressure with other structural measures of the eye, i.e. thickness of the macula or various macular layers.

Optical coherence tomography angiography (OCTA) is a novel non-invasive technique for imaging the neuronal and microvascular tissues of the retina and choroid. It has the potential to become an important screening and diagnostic tool for neuronal and vascular diseases beyond the eye. Prior studies have suggested that a past history of hypertension may be associated with reduced vessel density<sup>4</sup> though no study has been able to combine late-life OCTA data with measured blood pressure in mid-life, thus avoiding recall bias.

OCT, though now frequently used as a clinical tool, has seldom been studied in free-living populations. Understanding, in such a population, the long-term relationship of blood pressure to retinal OCT measures can help inform the ocular benefits (or risks) of early and persisting high/low blood pressure, and blood pressure treatment. Data could provide practical guidance regarding potential approaches to preventing eye disease.

1: Jung S, Bosch A, Kohler N, Ott C, Kannenkeril D, Dienemann T, Harazny JM, Michelson G, Schmieler RE. Evidence of neurodegeneration in individuals with only mildly elevated blood pressure. *J Hypertens*. 2019 Jun 24. doi:10.1097/HJH.0000000000002164. [Epub ahead of print] PubMed PMID: 31246897.

2: Jie R, Xu L, Wang YX, Zhang L, You QS, Yang H, Jonas JB. Ten-Year Incidence of Retinal Nerve Fiber Layer Defects: The Beijing Eye Study 2001/2011. *Invest Ophthalmol Vis Sci*. 2015 Aug;56(9):5118-24. doi: 10.1167/iovs.15-16682. PubMed PMID: 26241399.

3: Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Hypertension, perfusion pressure, and primary open-angle glaucoma. A population-based assessment. *Arch Ophthalmol*. 1995 Feb;113(2):216-21. PubMed PMID: 7864755.

4: Lee WH, Park JH, Won Y, Lee MW, Shin YI, Jo YJ, Kim JY. Retinal Microvascular Change in Hypertension as measured by Optical Coherence Tomography Angiography. *Sci Rep*. 2019 Jan 17;9(1):156. doi: 10.1038/s41598-018-36474-1. PubMed PMID: 30655557; PubMed Central PMCID: PMC6336859.

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

Using OCT and OCTA data from EyeDOC and baseline blood pressure measurements from ARIC, we will:

- 1) Examine the relationship of blood pressure measurements obtained at baseline and later ARIC visits – with structural measures of optic nerve/retinal damage, including RNFL thickness obtained from EyeDOC peripapillary OCT scans and total and layer-specific thickness obtained from EyeDOC macular scans.
- 2) Evaluate the relationship between blood pressure measurements obtained at baseline and later ARIC visits – with retinal vascular measures such as blood vessel density determined from OCTA scans obtained from EyeDOC.

**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 and Study population:**

We will use both historical data (baseline and the fourth ARIC visit) on blood pressure and blood pressure treatment as well as current (V6) blood pressure and blood pressure treatment data. Data regarding structural and vascular measures of the eye (OCT and OCTA data, respectively) will come from the EyeDOC visit, conducted between May 2017 and June 2019. Inclusion/Exclusion criteria: ARIC participants recruited in the EyeDOC ancillary study will be included. These include ~500 African-American participants with Mini-Mental State Examination (MMSE) scores no less than 22 from the Jackson study site and ~500 white participants with MMSE scores no less than 24 from the Washington County study site. Study population will include all participants in the EyeDOC study with interpretable OCT/OCTA data available, along with baseline blood pressure data. Non-white participants from Washington County and non-African-American participants from Jackson will be excluded.

**Primary outcome variables:** Primary structural outcomes of the eye will include total RNFL thickness derived from peripapillary OCT scans, and total and layer-specific thickness of the macula defined from macular OCT scans. Primary vascular measures of the eye will include vessel density from 4.5x4.5 mm peripapillary scans and from 3x3 or 6x6 mm macular scans.

**Primary blood pressure variables:** Hypertension (based on SBP, DBP and use of antihypertensive medications) and systolic and diastolic blood pressure values from the baseline ARIC visit (1987-9), the fourth visit (1993-5) and visit 6 (2016-7). We will also be interested in any associations with specific types of antihypertensive agents, realizing the difficulty of interpreting any associations found as causal in this observational study with little information on the indications considered for the drug prescriptions.

**Other variables of interest:** Data to be collected as possible confounders include age, race, gender, household income, education level; axial length, IOP, smoking history; comorbidities: diabetes, blood sugar/HgbA1c, cholesterol and triglycerides.

**Proposed analysis:** We will look at the association between presenting mid-life hypertension status (present vs. absent) and RNFL thickness, total macular thickness, and thickness of specific

macular layers, particularly the GC/IPL layer. As evidence exists for optic nerve damage at both elevated and low BP, associations across the range of BP will be explored with polynomials to check for nonlinearity and spline terms will be incorporated as appropriate. Initial analyses will examine the OCT parameters in relation to hypertension status, SBP level, and DBP level separately at three points: visit 1, visit 4, and visit 6.

Some evidence exists that low blood pressure (particularly that resulting from treatment/overtreatment of BP) may be a risk for optic nerve damage, and so additional analyses will be run to examine this hypothesis. Specific groups to be compared will include:

- 1) Normal blood pressure at V1, V4, and V6 (reference group)
- 2) Chronic midlife hypertension (systolic blood pressure >140 and/or diastolic blood pressure >90 at V1 and V4)
- 3) Low blood pressure (systolic blood pressure <90 or diastolic blood pressure <60) at V1, V4 or V6, or a 25% decline in systolic or diastolic blood pressure from V4 to V6.

All analyses will be performed in Jackson and Washington County center participants separately, and, unless associations are qualitatively different, in combination with adjustment for race.

**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 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 ICTDER 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 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/mantrack/maintain/search/dtSearch.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)?**

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**: 263-70.

Walker KA, Sharrett AR, Wu A, et al. Association of Midlife to Late-Life Blood Pressure Patterns With Incident Dementia. *JAMA* 2019; **322**(6): 535-45.

**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\* 2014.38)**

**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 <https://www2.csc.unc.edu/aric/approved-ancillary-studies>

**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.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.