1.a. Full Title: The association between arterial stiffness and incident heart failure and microvascular disease – an analysis from the ARIC Study

b. Abbreviated Title (Length 26 characters): Arterial Stiffness \& CHF/CKD

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*Co-authors will contribute equally to the work.

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

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3. **Timeline**: Analysis is to start as soon as approval is obtained. Manuscript is to be prepared as soon as analysis is available. We hope that the manuscript will be prepared within one year from approval of the analysis.

4. **Rationale**:

Arterial stiffness has been shown to be associated with cardiovascular outcomes (1). Recent studies have found a stronger association between arterial stiffness and incident stroke than CHD events (2-4), a pattern also seen with hypertension (5).

The process of arterial stiffening has been postulated to contribute to the development of hypertension, specifically the observed age-related increase in systolic and pulse pressures seen in general populations (6). In fact, its local measurement on carotid ultrasound has been linked to the development of hypertension (7) and incident stroke (ARIC MP#1461) in the ARIC study.

Thus, one would expect arterial stiffness to be associated with other sequelae of hypertension (e.g., renal insufficiency, retinal changes (i.e. arteriolar narrowing, A/V nicking, and retinopathy), heart failure) in addition to stroke. Furthermore, myocardial stiffness has been shown to be associated with heart failure (8). Arterial stiffness has been linked with myocardial stiffness in the form of left ventricular hypertrophy (9). However, the available clinical data on relation of arterial stiffness to incident kidney disease, retinopathy, and heart failure remain limited.

The purpose of this proposal is to examine the relationship of arterial stiffness measured with ultrasound to incident heart failure, renal disease, and retinopathy.

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

Hypotheses:
   a) Increased arterial stiffness is significantly associated with incident heart failure.
   b) Increased arterial stiffness is significantly associated with incident renal disease (i.e., incident chronic kidney disease or incident end-stage renal disease).
   c) Increased arterial stiffness is significantly associated with increased retinal arteriolar narrowing, incident A/V nicking and retinopathy.

Study Questions:
   a) Is arterial stiffness measured with carotid ultrasound associated with incident heart failure?
   b) Is arterial stiffness measured with carotid ultrasound associated with incident renal disease?
   c) Is arterial stiffness measured with carotid ultrasound associated with increased retinal arteriolar narrowing and incident retinopathy?

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)**.
A. Study Design
The analysis will be done at John Hopkins. The proposed study will be a retrospective cohort design using data acquired from all ARIC study centers. Participants with arterial stiffness measures derived from carotid ultrasounds at ARIC Visit 2 will be followed through [December 31, 2007] for incident heart failure, kidney disease, and Visit 4 for retinal changes.

B. Inclusions/Exclusions
1. Inclusions
Participants in ARIC visit 2 who had carotid ultrasounds done and arterial stiffness measures available will be included in the analysis.

2. Exclusions
   a. Standard ARIC exclusions (race exclusions for the different communities).
   b. Individuals with less than 2 cardiac cycles of arterial stiffness measures will also be excluded.
   c. Subjects with prevalent heart failure at the time of the carotid ultrasound will be excluded for the heart failure analysis. Individuals will be considered to have prevalent heart failure if they met any of the following criteria: heart failure hospitalization before visit 2, symptomatic heart failure using Gothenberg (stage 3) criteria and assessed at ARIC visit 1 or 2, or medication use for heart failure during those visits (10).
   d. Those with renal disease defined as glomerular filtration rate <60 mL/min/1.73 m² will be excluded for the renal disease analysis.
   e. Individuals missing covariate data of interest for a specific outcome (e.g., heart failure or chronic kidney disease, see Covariates) will be excluded from the analysis for that outcome.

C. Exposures
Each arterial stiffness measures will be examined as the exposure variable within each analysis. Arterial stiffness measures will include the following variables:

<table>
<thead>
<tr>
<th>Arterial stiffness Measure</th>
<th>Calculation (from ARIC Manual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid Arterial Strain (CAS) (%)</td>
<td>((DS – DD) / DD)</td>
</tr>
<tr>
<td>Arterial Compliance (AC) (mm³/kPa)</td>
<td>(\pi * (DS^2 – DD^2) / (4 * PP))</td>
</tr>
<tr>
<td>Arterial Distensibility (AD) (%/kPa)</td>
<td>(100 * (DS^2 – DD^2) / (PP * DD^2))</td>
</tr>
<tr>
<td>Stiffness Index (SI) (dimensionless)</td>
<td>(\ln (SBP / DBP) / CAS)</td>
</tr>
<tr>
<td>Pressure-strain modulus ((E_p)) (kPa)</td>
<td>(PP / CAS)</td>
</tr>
<tr>
<td>Young’s elastic modulus ((YEM)) (kPa)</td>
<td>((0.5 * DD / CIMT) * E_p)</td>
</tr>
</tbody>
</table>

\(DS = \text{peak systolic arterial diameter; } DD = \text{end diastolic arterial diameter; } SBP = \text{systolic blood pressure; } DBP = \text{diastolic blood pressure; } PP = \text{pulse pressure}\)
D. Covariates
Regression models (Statistical Methods) will be examined with and without adjustments for different covariates. Covariates common to all analyses will include:

1. Demographic variables: age, sex, race, socioeconomic status, study center
2. Anthropometric measurements: height, weight, body mass index
3. SBP measured during the ultrasound exam (in a separate model)

Covariates specific to the heart failure analysis will include variables in the ARIC heart failure model (under review).

Covariates specific to the kidney disease analysis and retinopathy analyses will include:
1. Smoking status, smoking intensity
2. Hypertension: Systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, antihypertensive medication use
3. Blood pressure: Systolic and diastolic blood pressures; supine, sitting, or at time of the ultrasound examination
4. Diabetes, fasting insulin, and glucose levels
5. Lipid parameters: low- and high-density lipoprotein cholesterol levels, triglycerides
6. History of stroke and/or CHD
7. Family history of premature CHD

Covariates specific to the kidney disease analysis will include baseline creatinine levels.

E. Outcomes

Heart Failure: Participants were not asked about clinical symptoms at visits 3 and 4; thus, symptomatic heart failure cannot be assessed at these visits. However, intervening heart failure hospitalizations are available.

In individuals free of heart failure at baseline (visit 2), incident heart failure will be defined as the first heart failure hospitalization or death from heart failure for those without a prior heart failure hospitalization. Heart failure diagnosis will be established using International Classification of Disease, Ninth Revision (ICD-9) code 428 or Tenth Revision (ICD-10) code I50 in the first position. Additionally, to improve sensitivity of our outcome, we will perform a secondary analysis using a definition of heart failure based on ICD-9 code 428 in any position, as in previous ARIC studies. Individuals will be followed through January 1, 2006 (10).

Kidney disease: We will define incident kidney disease based on an glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² estimated from serum creatinine measured at Visits 3 and 4, an incident hospitalization (discharge or death) coded for chronic renal disease (ICD-9 codes 581-583 or 585-588), hypertensive renal disease (ICD-9 code 403), hypertensive heart and renal disease (ICD-9 code 404), unspecified disorder of kidney and ureter (ICD-9 code 593.9), diabetes with renal manifestations (ICD-9 code 250.4), kidney transplantation, renal dialysis, or adjustment/fitting of catheter (ICD-9 codes V42.0, V45.1, or V56), hemodialysis (ICD-9 code 39.95) or peritoneal dialysis (ICD-9
code 54.98), without acute renal failure (ICD-9 codes 584, 586, 788.9, or 958.5) as the primary or secondary hospitalization code with follow-up to 2008 or most recent hospitalization files available. We will also examine the visit-based GFR and hospitalization-based definitions separately to assess whether any observed associations are similar and compare MDRD and CKD-EPI equations for estimation of GFR. At ARIC Visit 4, we also have information on urinary albumin, urinary creatinine, and serum cystatin C that will be used in sensitivity analyses to identify additional cases of kidney disease.

*Retinal Disease:* Retinal photographic data are available for all participants at Visit 3 (1993-95) and a subsample of 1,034 participants at Visit 4 (1996-98). Trained graders evaluated retinal photographic slides for focal lesions, including signs typical of diabetic retinopathy, including both background and proliferative retinopathy (e.g., microaneurysms, retinal hemorrhages, hard exudates and/or cotton wool spots) according to a standardized protocol. The main retinal outcomes of interest will be arteriolar narrowing, A/V nicking, and any retinopathy at Visit 3 in the absence of other retinal vascular causes, e.g., retinal vein occlusion. Secondary analyses will be conducted to examine the associations of arterial stiffness measures with specific retinal findings and disease severity. We will also examine the relationship between arterial stiffness measures and change in arteriolar narrowing and progression of retinopathy (defined at two steps or more along the ETDRS severity scale) in the N=981 participants who had retinal photographs at both Visits 3 and 4.

**F. Statistical Methods**

Each arterial stiffness parameter will be modeled both as continuous variables and as quartiles. Appropriate parametric and non-parametric tests of comparison will be used to compare baseline characteristics. Baseline characteristics will also be examined for trends.

The association of arterial stiffness measures with incident heart failure and kidney disease will be examined using Cox proportional hazard models. Kaplan-Meier analysis will also be performed for incident heart failure and kidney disease.

The change in calculated eGFR between Visit 2 and Visit 4 will also be modeled as a dependent continuous variable using linear regression models.

The association of arterial stiffness measures with incident retinopathy will be examined using logistic regression models.

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.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)?

   A. Arterial stiffness
   MS #003A – Relationship of arterial stiffness and CVD risk factors

   MS #003B – Variation of CCA elasticity with IMT

   MS #003C – Association of distensibility and carotid wall thickness in healthy middle-aged adults

   MS #003D – Hypertension and arterial wall stiffness

   MS #003E – Type 2 diabetes mellitus, fasting glucose, insulin concentrations associated with arterial stiffness

   MS #087 – Arterial wall thickness, distensibility, prevalent disease

   MS #462 – Carotid artery size, stiffness versus incident events

   MS #510 – Multiple metabolic syndrome (disorder) and arterial stiffness

   MS #513 – Association of arterial stiffness and cerebrovascular diseases

   MS #723 – Association of ethnicity and vascular stiffness

   MS #928 – Vascular capacity and multiple metabolic syndrome
MS #1461 – Arterial stiffness and incident CVD

B. Incident Heart Failure
MS #927 – Heart failure incidence and survival: 13 year follow up of the ARIC cohort

MS #1118 – Kidney Function as a Risk Factor for Heart Failure Hospitalization: The ARIC Study

MS #1197 – Albuminuria as a Predictor of Incident Heart Failure Hospitalization and Mortality in the Atherosclerosis Risk in Communities (ARIC) Study

MS #1342 – The preventable burden of heart failure due to obesity and hypertension: the Atherosclerosis Risk in Communities (ARIC) study

MS #1376 – Optimal predictors of incident hospitalized heart failure: the ARIC cohort study.

MS #1475 – Hypertension, left ventricular hypertrophy, and risk of incident hospitalized heart failure: The ARIC study

C. Incident Kidney Disease
MS #1245 – Glycemic Control (HbA1c) and Incident Chronic Kidney Disease in Diabetes: The Atherosclerosis Risk in Communities Study

MS #1252 – Non-Diabetic Glycemia (HbA1c) and Incident Chronic Kidney Disease: The Atherosclerosis Risk in Communities Study

MS #1332 – Orthostatic hypotension and incident chronic kidney disease

MS #1348 – Chronic kidney disease and risk of hospitalization: The Atherosclerosis Risk in Communities Study

MS #1529 – Hemoglobin A1c (HbA1c) Cut-points and Risk of Kidney Disease and Prevalent Retinopathy

D. Retinopathy
MS #339 – Arteriolar narrowing and BP

MS #873 – Incidence, progression and regression of retinal arteriolar disease in the ARIC

MS #1234 – 10-year Incidence, Progression and Regression of Retinal Vascular Abnormalities and their Relationship with Vascular and Inflammatory Risk Markers

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