ARIC Manuscript Proposal #2027

PC Reviewed: 10/9/12  Status: A  Priority: 2
SC Reviewed:  _________  Status:  _____  Priority:  ____

1. a. Full Title: Retinopathy, P wave indices, and Atrial Fibrillation Incidence: the ARIC Study

   b. Abbreviated Title (Length 26 characters): Retinopathy and AF

2. Writing Group:

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

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3. Timeline:

   Data analysis: 4-5 months from manuscript approval date.
   First draft of the manuscript: 6-7 months from the manuscript approval date.
4. Rationale:

Atrial fibrillation (AF) is a major and growing public health problem with 3 million prevalent cases now and projected to double by 2050[1]. AF has been implicated in the causation of ischemic stroke, heart failure, early dementia, early death, and is associated with high health-care expenditures [2]. Although few common and early risk factors such as obesity, hypertension and diabetes account for about 40% of the modifiable risk [3], little is known about the role of coronary micro-vascular disease as a risk factor for AF.

The techniques to evaluate both coronary blood flow and reserve, which have developed over last two decades, include PET/CT (insensitive to functional impairment), and invasive methods are limited to clinical settings. Whereas retinal micro-vascular changes, which may be associated linearly with decrease in coronary flow reserve [4], are available at ARIC visit 3 for most of the cohort participants and a selected sample at the CarMRI study.

Increased left atrial (LA) dimension is one of the strongest echocardiography correlates of future AF risk. Also, AF is common among patients with heart failure (both with reduced and preserved EF). This indicates a possible role of increased left ventricular end-diastolic pressure (LVEDP) in atrial remodeling and potential induction of AF. In this context, retinopathy, a potential direct, non-invasive marker of micro-vascular injury is associated with higher LV mass and increased LA dimensions [5], concentric remodeling of the LV[6], and a 2.5 fold increase in HF incidence independent of strong confounders including diabetes and hypertension [7]. Lastly, albuminuria - a marker of renal micro vessel injury, has been associated with a two to three-fold increase in the risk of atrial fibrillation [8].One possible mechanism may be a higher predisposition of cardiac ischemia and intermittent diastolic dysfunction (as seen with flash pulmonary edema) in patients with micro-vascular disease. Also, atrial fibrosis has been shown to cause isolation of groups of atrial muscle and induction of electrical heterogeneity, thus forming the substrate for AF [9]. A strong association of endothelial dysfunction with AF has been contemplated though with unclear temporal relationship[10]. A possible mechanism might be retinopathy and AF may share common risk factors with endothelial dysfunction. Another possible mechanism is an increase in atrial fibrosis with microvascular changes in cardiac tissue; however this remains unstudied.

To the best of our knowledge, the association between retinopathy or other micro-vascular alterations in the retina (AV nicking, focal or global arteriolar narrowing) with atrial fibrillation have not been previously studied. Thus, we propose to study the relationship of these retinal micro-vascular signs with AF and P wave indices in persons with and without diabetes in a biracial, population-based cohort of middle-aged persons from four US communities.

5. Main Hypothesis/Study Questions:
- To evaluate the relationship of retinopathy and, other measures of retinal microvasculature alteration with atrial fibrillation.
- To explore the above association by race, gender, diabetes status, hypertension status, chronic kidney disease and albuminuria after adjustment for appropriate confounders.
- We will also explore the relationship of retinopathy with the abnormal P wave indices including P-wave terminal force, P-wave duration, P-wave area, and PR duration which are considered as markers of atrial substrate and conduction leading to AF.

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 methodological limitations or challenges if present).

Study design:
Time to event analysis using ARIC visit 3 as baseline. Visit 3 was used as the baseline because retinal photographs were obtained at this visit.

Exclusion criteria:
(1) Prevalent AF or atrial flutter at baseline based on electrocardiogram (ECG) or diagnosed incident AF before/at V3, (2) missing baseline ECG data, (3) missing retinal photographs or ungradeable (CRVO etc.), (4) missing other covariates, (5) race other than white or African-American, and (6) non-whites from the Minnesota and Washington County sites.

Variables of interest:

Main outcome of interest: Atrial fibrillation
The time to incident AF cases from baseline through December 31, 2009 will be the outcome variable. Incident AF cases were ascertained from three sources: ECGs completed during the study exams, ICD-9 codes of 427.31 or 427.32 from hospital discharges, and death certificates that include AF as a cause of death (ICD-9 code 427.3 or ICD-10 code I48). AF incidence date will be defined as the date of the first ECG showing AF, the first hospital discharge date for an AF or atrial flutter diagnosis, or date when death occurred due to AF, whichever occurred first.

Secondary outcome of interest: P wave indices
P-wave terminal force, P-wave duration, P-wave area, and PR duration

Main Exposure:
Retinopathy (yes vs. no), its severity, and its most frequent constituent signs (retinal hemorrhage and micro-aneurysms)

Other Exposures:
- Focal retinal microvascular changes (AV nicking, focal arteriolar narrowing).
- Generalized arteriolar narrowing: CRAE (central retinal arteriolar equivalent),
- CRVE (central retinal venular equivalent).

Covariates
From visit 3, other measured covariates to be included in the analysis are age, gender, race, study site, body mass index (BMI), height (a strong predictor of AF independently of BMI), drinking status, diabetes mellitus, albumin-creatinine ratio, eGFR, educational level, smoking status and cigarette-years, systolic blood pressure, use of antihypertensive medications, aspirin, warfarin, steroids, HbA1c, and a history of HF, myocardial infarction (MI), or stroke, incident heart failure, incident CHD. HbA1C from visit 2, glucose challenge test from visit 4.

Statistical analysis:
Cox proportional hazards models will be used to determine the association between the retinal measures and incident AF. We will test for interactions and include stratified analysis by race, gender, diabetes status, hypertension status, prevalent CHD, and prevalent CHF. We will also do sub-set analysis after excluding those with prevalent diabetes, hypertension, heart failure, or CHD. Analyses will use sequential models:

- Model 1: adjustment for age, gender, race, and ARIC study site
- Model 2: Model 1 + adjustment for BMI, height, diabetes mellitus, fasting blood glucose level, systolic blood pressure (at current and prior visits), use of antihypertensive medications, educational level, smoking status and cigarette-years, drinking status,
- Model 2.a Model 2 + HbA1c from visit 2.
- Model 3: Model 2 + history of heart failure, MI, and stroke
- Model 4: Model 3 + albuminuria, eGFR
- Model 5: Model 4 + incidence of heart failure, MI, and stroke as time-dependent covariates

Multiplicative effect modification will also be evaluated by age, gender, race, albuminuria, and CKD categories by conducting stratified analysis and including multiplicative terms between the effect modifier and retinopathy in the models.

We expect to observe more than 1200 incident AF events, which will provide sufficient power to study the association of retinopathy, and other microvascular alteration with incident AF. However, limited power might exist to study race-specific associations, particularly in African Americans and for stratified analysis.

Strengths and limitations:
The limitation of the ARIC retinal exam to one eye limits its sensitivity to the less frequent focal arteriolar changes. Another limitation is that most of the AF cases are identified from hospital discharge diagnosis. Thus, patients with AF who died out of hospital prior to first hospitalization with ICD code would not be captured including
those seen in outpatient settings. The exploration of association of retinopathy with P wave indices will provide more information in the settings of limitations of AF ascertainment as outlined above.

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

   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/search.php
   X Yes, no overlap found. _______ 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)?

    No previous manuscript proposals in ARIC have specifically examined the association between retinopathy and AF. Other ARIC manuscripts have explored the association between retinopathy and other outcomes.

    #855: Retinopathy and stroke
    #1222: Retinopathy and cognitive decline
    #964: Retinopathy and stroke
    #1432: Retinopathy, and MRI Brain abnormalities

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  X Yes  ____ No

    b. If yes, is the proposal
A. primarily the result of an ancillary study (list number*)

X B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2008.12)

*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: