ARIC Manuscript Proposal #2037

PC Reviewed: 11/12/12  Status: A  Priority: 2
SC Reviewed: _________ Status: _____ Priority: ____

1. a. Full Title: Retinopathy, ECG abnormalities, hsTNT, and sudden cardiac death: the ARIC Study
   b. Abbreviated Title (Length 26 characters): Retinopathy and SCD

2. Writing Group:

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

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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).

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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:**

More than 4/5th of all natural and unexpected deaths occurring within 2 hours of symptoms onset, occurs outside health systems, and have a cardiac cause[1]. Most of these Sudden Cardiac Deaths (SCDs) are preceded by arrhythmias (91%)[2, 3]. Most of the SCDs are believed to be related to ischemic heart disease. Also, patients with previous SCDs and reduced left ventricular ejection fractions (LVEF) are at increased risk. Other causes of SCD such as cardiomyopathies (HCM, ARVC), rare genetic mutations (long QT, Brudada) etc. are less common and typically presents at a younger age. For middle aged adults, the risk factors for SCD beyond macro-vascular disease remain unclear. In this context, the relationship of micro-vessel disease with SCD has not been studied.

Micro-vascular disease may contribute to or aid in precipitation of SCD through several mechanisms including cardiac cellular apoptosis leading to tissue heterogeneity, baseline ECG abnormalities, myocardial ischemic currents, electrolyte abnormalities through nephropathy etc. (Figure 1 on page 4 below). The techniques to evaluated coronary microvascular disease are invasive (use of catheterization), costly (PET/CT), and improving in terms of validity thus are not available to the population based studies. In this regards, microvascular changes seen in other organ systems such retinopathy or micro-albuminaria, which are non-invasive and measured in population based study may serve as proxy of coronary microvascular changes (unstudied).

Retinopathy is associated with higher LV mass and increased LA dimensions [4], concentric remodeling of the LV[5], and a 2.5 fold increase in HF incidence independent of strong confounders including diabetes and hypertension [6]. As compared to non-diabetics, diabetics with concurrent retinopathy had 170% higher risk of SCD, and diabetics without retinopathy had 70% higher risk of SCD[7]. Microvascular disease as evidenced by albuminaria has been shown to be associated with SCD in diabetics [8]. One study result indicated that while glycemia control had improved the risk of macrovascular deaths the risk of SCD was only slightly altered [9]. Also, ARIC study didn’t find any differences in the relative risks of SCD vs. non-fatal AMI by diabetes status [10] – though absolute risks will differ greatly given lower absolute risk of SCD than non-fatal MI – this finding may point to macrovascular diseases as a major contributor to both types of events.

In addition to the relationship of the microvascular disease with hard events, its relationship with proxies such as detectable troponin in serum and ECG abnormalities may provide some insights into pathways. In this context, the absence of macrovascular disease in a higher proportion of women presenting with anginal pain called cardiac syndrome X may be important. An unpublished report by Rautaharju et. al. found that different ECG parameters associated with SCD differed greatly by gender. Higher cardiac apoptosis as evidenced by troponin T >100ng/L was seen with retinopathy among patients on dialysis (73% in those with retinopathy vs. 21% in those without)[11]. Other
pathologies, such as severe pulmonary hypertension also leads to higher troponin detection in serum [12], and portends a higher risk of SCD.

To the best of our knowledge, the association between retinopathy or other microvascular alterations in the retina (AV nicking, focal or global arteriolar narrowing) with SCD have not been previously studied. Thus, we propose to study the relationship of these retinal micro-vascular signs and albuminuria with SCD in the ARIC cohort study by gender, diabetes, and hypertension status. Also, we will explore the relationship of micro-vessel disease with cross sectional ECG abnormalities, and troponin leak by gender, diabetes status, and hypertension status.

Figure 1. A schematic diagram of study hypotheses. The yellow and orange boxes are the study’s focus. Black box measures are not available in the ARIC study.
5. **Main Hypothesis/Study Questions:**

We hypothesize the micro-vascular disease will have similar or stronger relationship with SCD than non-fatal MI after adjusting for potential confounders. Micro-vascular disease is associated with increased cardiac apoptosis thus elevated serum troponin and ECG abnormalities which may act as intermediaries to micro-vascular disease and SCD. These associations may be stronger in female than male.

1. To study the relationship of micro-vessel disease markers (retinopathy and micro-albuminaria) with sudden cardiac death and contrast it with non-fatal MI
   a. by gender, diabetes, hypertension, and CHD status

2. Cross sectional analysis of retinopathy with ECG parameters and hs-TNT:
   a. To evaluate the relationship of retinopathy and ECG abnormalities that has been shown to portend higher risk of sudden cardiac death by gender.
   b. To explore evaluate the relationship of retinopathy at V3 with detection of hs troponin T at V4 by gender, micro-albuminaria at V4, and diabetes (and its severity/control).

3. To study the relationship between hs-TNT and risk of SCD and non fatal-MI by prevalent CHD status

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** will vary by specific aims:
Common to all: missing retinal photographs or ungradeable (CRVO etc.), missing covariates,
Aim 1. Those with missing information on important covariates
Aim 2a and 2b. Those with missing/poor information on ECG and hsTNT, respectively
Aim 3. Those with missing information on important covariates

**Variables of interest:**

*Main outcome of interest: Sudden Cardiac Death*
A physician panel has adjudicated SCD as sudden death, a pulseless condition without a known non-cardiac cause, or death determined by death certificate codes indicating death due to underlying heart disease that occurred outside the hospital or in the emergency department through 2004. We will contrast the risk of SCD with risk of non-sudden cardiac deaths and also with non-fatal MI.

Secondary outcome of interest: hsTNT and ECG abnormalities
Troponin T assayed using a high sensitivity assay at ARIC visit 4.

ECG abnormalities known to be related to arrhythmogenic substrate: 1) QRS duration; 2) Rate-adjusted QT interval (QTea); 3) Global dispersion of repolarization defined as the interval between Tpeak (Tp) and Tend (Te) (Tp-Te); 4) Heart rate variability (SDNN); 5) Spatial angle between the mean QRS and T vectors (Θ(QRS|T)); 6) QRS nondipolar components from singular value decomposition (RNDPV); 7) The ratio of To and Tp spatial vector magnitudes (ToV/TpV); 8) T amplitude in aVR; 9) T amplitude in aVL

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

Secondary Exposure
Albuminaria at visit 4 (albumin to creatinine ratio in spot urine)

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, incidental 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 microvascular changes (retinal measures and and albuminaria) with SCD and contrast it with non-fatal MI using multivariate analysis. We will test for interactions and include stratified analysis by race, gender, diabetes status, hypertension status. Combined effect of retinopathy and albuminaria will be studied by creating 6 categories by cross of albuminaria categories (We will also do sub-set analysis after excluding those with
prevalent diabetes, hypertension, heart failure, or CHD. Analyses will use sequential models for aim 1.

- Model 1: adjustment for age, gender, race*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 + eGFR
- Model 5: Model 4 + incidence of heart failure and CHD as time-dependent covariates

Aim 2a and 2b are cross-sectional analysis exploring the relationship between retinopathy (its severity) with serum hsTnT and similarly between albuminaria and hsTnT.

Aim 3 is time to SCD analysis using V4 troponin as exposure (meaningful categories after using splines)

We expect to observe more than 150 sudden cardiac death events through 2002, which may provide sufficient power to study the association of retinopathy, and other micro-vascular alteration with SCD. However, limited power may be available to study gender specific associations, particularly among women and for stratified analysis. We will start with a gender interaction term with retinopathy variable and if this is significant will try to stratify.

Strengths and limitations:

The limitation of the ARIC retinal exam to one eye limits its sensitivity to the less frequent focal arteriolar changes. Also, SCD has not been evaluated past 2002, thus limiting the power to study this. The use of multivariate model and competing risk analysis will add some strength when teasing this out.

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.cscc.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/micro-albuminuria and SCD/ECG changes/hsTnT. 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
   #1497: Retinopathy and AF

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.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: