ARIC Manuscript Proposal #2202

PC Reviewed: 8/13/13  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title: Novel Kidney Filtration Markers and Incident Sudden Cardiac Death: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): B2M, BTP, Cystatin C, and SCD

2. Writing Group:
   Writing group members:
   Takeki Suzuki, MD, MPH, PhD; Kunihiro Matsushita, MD, PhD; Sunil Agarwal, MD, PhD, MPH; Morgan Grams, MD, PhD; Elizabeth Selvin, PhD; MPH, Hugh Calkins, MD; Josef Coresh, MD, PhD; others welcome

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

   First author: Takeki Suzuki, MD, MPH, PhD
   Address: Division of Cardiology / Department of Medicine
            The Johns Hopkins Hospital
            600 N. Wolfe Street, Carnegie 568
            Baltimore, Maryland 21287

            Phone: 410-614-2000  Fax: 410-502-4854
            E-mail: tsuzuki5@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: Kunihiro Matsushita, MD, PhD
   Address: Department of Epidemiology
            Johns Hopkins Bloomberg School of Public Health
            615 N. Wolfe Street (Rm W6017), Baltimore, MD 21205

            Phone: (443) 287-8766  Fax: (443) 683-8358
            E-mail: kmatsus5@jhmi.edu

3. Timeline:
Data to be used in this proposal are currently available. Analyses and manuscript preparation will be performed over the next 6 months.

4. **Rationale:**

Sudden cardiac death (SCD), defined as a sudden and unexpected pulseless condition with cardiac etiology, has been a public health issue worldwide. In the U.S., the annual SCD cases are estimated at 300,000 - 350,000, accounting for 15 percent of annual mortality. Since SCD can occur out-of-hospital before any medical care can be given to the patients, there is a need to identify individuals at high risk and to prevent SCD. It is known that most SCD cases (up to 80%) have coexisting coronary artery disease. Currently, decreased ejection fraction (EF) is the only variable used clinically for SCD risk stratification, and implantable cardioverter defibrillator has been shown to reduce SCD risk among the patients with this condition (EF ≤ 35%). However, this subgroup only accounts for 20% to 30% of SCD and there remains a need to investigate on risk factors for future occurrence of SCD.

Chronic kidney disease (CKD) is a well-known risk factor of cardiovascular disease and mortality. It has been recently shown that individuals with CKD had similar mortality risk to those with prior myocardial infarction. Indeed, European clinical guidelines recognized CKD as a cardiovascular risk equivalent. However, little is known about the association between CKD and SCD, despite potential mechanisms linking CKD to SCD, e.g., electrolyte disturbances such as potassium.

Glomerular filtration rate (GFR) is the best overall measure of kidney function and is usually estimated using serum creatinine in clinical practice and epidemiological research. On the other hand, it is well known that serum creatinine is affected by muscle mass. In this context, several novel markers of kidney function such as cystatin C demonstrate some advantages over serum creatinine in terms of cardiovascular risk prediction. Thus, the objective of this study is to investigate the relationship of three novel kidney filtration markers, β2-microglobulin (B2M), β-trace protein (BTP), and cystatin C, to the incidence of SCD in the ARIC Study. We are particularly interested in B2M, since B2M outperformed cystatin C for predicting mortality in some studies.

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

**Hypothesis 1:** Higher B2M, BTP, and Cystatin C are independently associated with incident SCD.

**Hypothesis 2:** Among these three kidney measures, B2M is most strongly associated with incident SCD.

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: prospective cohort study

Inclusions:
Primary analysis: All ARIC subjects with data of B2M, BTP and cystatin C at visit 4
Secondary analysis: All ARIC subjects with data of B2M and cystatin C at visit 2 (BTP is not available in all participants at Visit 2)

Exclusions:
Subjects without data of B2M, BTP, or cystatin C
Non-black and non-white participants

Exposures of interest:
B2M, BTP, and cystatin C measured at visit 4 (measured as part of Ancillary Study #2006.16) and B2M and cystatin C measured at visit 2 (measured as part of Dr. Selvin’s Ancillary Study #2009.16). We will also evaluate eGFR estimated from cystatin C using the CKD-EPI cystatin C equation.18

Outcome:
Incident SCD: All events classified as having fatal coronary heart disease (CHD) were reviewed. SCD is defined as a sudden pulseless condition presumed to be due to a ventricular tachyarrhythmia in a previously stable individual without evidence of a noncardiac cause of cardiac arrest. After review of data available, cases were classified as definite sudden arrhythmic death, possible sudden arrhythmic death, not sudden arrhythmic death, or unclassifiable. For this analysis, SCD was defined as definite or possible sudden arrhythmic deaths.19, 20

Other variables of interest and covariates:
Sociodemographics: age, race/center, gender, education, income
Physical information: blood pressure, body mass index, presence/absence of left ventricular hypertrophy by electrocardiogram and carotid atherosclerosis by ultrasound
Lifestyle: smoking status and alcohol consumption
Comorbidities: hypertension, diabetes mellitus, dyslipidemia, history of CHD, albuminuria

Statistical Analysis Plan:
Cox proportional hazards models will be used to evaluate associations among B2M, BTP, cystatin C, and incident SCD. B2M, BTP, and cystatin C will be treated as categorical (quartiles) and continuous variables in the models. We will adjust for the covariates listed above. Regarding the strength of association across novel kidney markers, coefficients for a given quartiles (e.g., top quartile) or for 1-SD increment of each kidney marker will be compared.

Since eGFR based on serum creatinine (eGFRcr) is being explicitly analyzed in MP #1244, we will take eGFRcr into account in a few sensitivity analyses. Specifically, we...
will assess whether the associations of three novel filtration markers with SCD are independent of eGFRcr and stronger than that of eGFRcr.

Given the availability of BTP as an exposure and albuminuria as a key covariate, our primary analysis will use data obtained at visit 4. Secondary analysis with data at visit 2 will allow us to test robustness of our findings with more SCD cases during longer follow-up time.

Limitations:
First, a number of SCD cases after visit 4 may be limited. Second, our definition of SCD was based on adjudicated fatal CHD. Other etiologies of SCD such as inherited rhythm disorders might have not been detected by our SCD definition. Third, there will remain a possibility of residual confounding although we adjust for variables that are known to be associated with SCD. Lastly, the analysis primarily relies on a single measurement of key exposures, and there is a chance of misclassification due to short-term variability. However, we will repeat our analysis using values derived from visit 2 and visit 4.

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 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 _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.cscce.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)?
The most related proposal is MP1244# titled “Kidney dysfunction and Sudden Cardiac Death among Participants in the ARIC Study”. The key authors of this proposal, Sunil Agarwal and Josef Coresh, are included in the current proposal. There are a few more relevant proposals, but our angle of research hypothesis is different with that in those proposals.

- MP 1888, “Assessment of Conventional Cardiovascular Risk Factors and Multiple Biomarkers for the Prediction of Sudden Cardiac Death”
  - Cystatin C is included in the panel of novel biomarkers along with hs-CRP, NT-proBNP, and cTnT.
  - The main question is improvement in prediction of SCD
  - B2M and BTP are not included

- MP 2037, “Retinopathy, ECG abnormalities, hsTnT, and sudden cardiac death: the ARIC Study”
  - Albuminuria is one of the key exposures (a covariate in our proposal)

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

11.b. If yes, is the proposal

  _X_  A. primarily the result of an ancillary study (list number* ___ list ancillary number for ARIC-CKD grant here; and AS#2009.16 (PI: Selvin) ___)

  ____ 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/](http://www.cscc.unc.edu/aric/forms/)

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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.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.

Reference List


