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]**

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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.[1] In the U.S., the annual SCD cases are estimated at 300,000 - 350,000[2], accounting for 15 percent of annual mortality.[3, 4] 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 diease.[5] 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 ($EF \leqq 35\%$) .[6] However, this subgroup only accounts for 20% to 30% of SCD[7, 8] and there remains a need to investigate on risk factors for future occurrence of SCD.[1]

Chronic kidney disease (CKD) is a well-known risk factor of cardiovascular disease and mortality.[9, 10] It has been recently shown that individuals with CKD had similar mortality risk to those with prior myocardial infarction[11] . Indeed, European clinical guidelines recognized CKD as a cardiovascular risk equivalent.[12] 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.[13] On the other hand, it is well known that serum creatinine is affected by muscle mass.[14] 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.[15, 16] Thus, the objective of this study is to investigate the relationship of three novel kidney filtration markers, β_2-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.[17]

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.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)?

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 Biomakers 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/

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.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

Reference List

1. Fishman GI, Chugh SS, Dimarco JP, Albert CM, Anderson ME, Bonow RO, Buxton AE, Chen PS, Estes M, Jouven X, Kwong R, Lathrop DA, Mascette AM, Nerbonne JM, O'Rourke B, Page RL, Roden DM, Rosenbaum DS, Sotoodehnia N, Trayanova NA, Zheng ZJ. Sudden cardiac death

prediction and prevention: Report from a national heart, lung, and blood institute and heart rhythm society workshop. *Circulation*. 2010;122:2335-2348
2. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: Epidemiology, transient risk, and intervention assessment. *Annals of internal medicine*. 1993;119:1187-1197
3. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Blanc JJ, Budaj A, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL, Smith SC, Jr., Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B. Acc/aha/esc 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A report of the american college of cardiology/american heart association task force and the european society of cardiology committee for practice guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death) developed in collaboration with the european heart rhythm association and the heart rhythm society. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2006;8:746-837
4. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the united states, 1989 to 1998. *Circulation*. 2001;104:2158-2163
5. Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation*. 1998;98:2334-2351
6. Russo AM, Stainback RF, Bailey SR, Epstein AE, Heidenreich PA, Jessup M, Kapa S, Kremers MS, Lindsay BD, Stevenson LW. Accf/hrs/aha/ase/hfsa/scai/scct/scmr 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: A report of the american college of cardiology foundation appropriate use criteria task force, heart rhythm society, american heart association, american society of echocardiography, heart failure society of america, society for cardiovascular angiography and interventions, society of cardiovascular computed tomography, and society for cardiovascular magnetic resonance. *Journal of the American College of Cardiology*. 2013;61:1318-1368
7. de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, van Ree JW, Daemen MJ, Houben LG, Wellens HJ. Out-of-hospital cardiac arrest in the 1990's: A population-based study in the maastricht area on incidence, characteristics and survival. *Journal of the American College of Cardiology*. 1997;30:1500-1505
8. Stecker EC, Vickers C, Waltz J, Socoteanu C, John BT, Mariani R, McAnulty JH, Gunson K, Jui J, Chugh SS. Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: Two-year findings from the oregon sudden unexpected death study. *Journal of the American College of Cardiology*. 2006;47:1161-1166
9. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: A collaborative meta-analysis. *Lancet*. 2010;375:2073-2081
10. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *The New England journal of medicine*. 2004;351:1296-1305
11. Tonelli M, Muntner P, Lloyd A, Manns BJ, Klarenbach S, Pannu N, James MT, Hemmelgarn BR. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: A population-level cohort study. *Lancet*. 2012;380:807-814
12. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvanne M, Scholte op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The fifth joint task force of the european society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *European heart journal*. 2012;33:1635-1701
13. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function--measured and estimated glomerular filtration rate. *The New England journal of medicine*. 2006;354:2473-2483

14. Astor BC, Levey AS, Stevens LA, Van Lente F, Selvin E, Coresh J. Method of glomerular filtration rate estimation affects prediction of mortality risk. *Journal of the American Society of Nephrology : JASN*. 2009;20:2214-2222
15. Peralta CA, Shlipak MG, Judd S, Cushman M, McClellan W, Zakai NA, Safford MM, Zhang X, Muntner P, Warnock D. Detection of chronic kidney disease with creatinine, cystatin c, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. *JAMA : the journal of the American Medical Association*. 2011;305:1545-1552
16. Astor BC, Shafi T, Hoogeveen RC, Matsushita K, Ballantyne CM, Inker LA, Coresh J. Novel markers of kidney function as predictors of esrd, cardiovascular disease, and mortality in the general population. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2012;59:653-662
17. Shinkai S, Chaves PH, Fujiwara Y, Watanabe S, Shibata H, Yoshida H, Suzuki T. Beta2-microglobulin for risk stratification of total mortality in the elderly population: Comparison with cystatin c and c-reactive protein. *Archives of internal medicine*. 2008;168:200-206
18. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS. Estimating glomerular filtration rate from serum creatinine and cystatin c. *The New England journal of medicine*. 2012;367:20-29
19. Peacock JM, Ohira T, Post W, Sotoodehnia N, Rosamond W, Folsom AR. Serum magnesium and risk of sudden cardiac death in the atherosclerosis risk in communities (aric) study. *American heart journal*. 2010;160:464-470
20. Chen LY, Sotoodehnia N, Buzkova P, Lopez FL, Yee LM, Heckbert SR, Prineas R, Soliman EZ, Adabag S, Konety S, Folsom AR, Siscovick D, Alonso A. Atrial fibrillation and the risk of sudden cardiac death: The atherosclerosis risk in communities study and cardiovascular health study. *JAMA internal medicine*. 2013;173:29-35