ARIC Manuscript Proposal # 1888

PC Reviewed: 2/14/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Assessment of Conventional Cardiovascular Risk Factors and Multiple Biomarkers for the Prediction of Sudden Cardiac Death

b. Abbreviated Title (Length 26 characters): Prediction of Sudden Cardiac Death

2. Writing Group:

Writing group members: Rajat Deo, Suma Konety, Selcuk Adabag, Alvaro Alonso, Ronit Katz, Nona Sotoodehnia, Brian Kestenbaum, David Siscovick, Mike Shlipak, Christie M. Ballantyne, Aaron Folsom

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _RD_ **[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:

After manuscript proposal has been accepted, we anticipate the following timeline:
Analyses: 2 months
Preparation of manuscript: 1 month

4. Rationale:

Multiple studies have evaluated a host of noninvasive and invasive measures to identify high-risk patients at risk for ventricular arrhythmias and sudden cardiac death (SCD).[1-3] The majority of these risk stratification efforts have been directed

toward patients with advanced cardiomyopathies.[4] These studies have demonstrated consistently that impaired left ventricular function identifies patients at an increased risk for ventricular arrhythmias and death. Most SCD events, however, occur in the general population[5-7] where prediction algorithms have not been evaluated systematically.

Recently, our group evaluated SCD prediction among women with coronary artery disease in whom the overall rate of SCD was less than that observed in populations with established cardiomyopathies. Our findings demonstrated that the combination of clinical risk factors and LVEF (C-index 0.681) was a better predictor of SCD events than LVEF alone (C-index 0.600). [8] While clinical characteristics in this study substantially improved risk prediction, the C-index of 0.681 for the combined model is still relatively low suggesting that additional variables including biological markers need to be evaluated to better stratify higher risk populations who do not yet have a LVEF < 35%.

Several epidemiologic studies have elucidated potential mechanisms in the SCD pathway by evaluating the independent associations between biomarkers and SCD in population-based studies.[9-12] No study, however, has assessed whether the inclusion of any individual or combination of biomarkers in a model based on clinical risk factors results in a more accurate risk assessment and prediction. The identification of novel risk predictors early in the natural history of conditions predisposing to SCD is an important epidemiological task that has been prioritized by the National Heart, Lung, and Blood Institute.[13]

In this population-based sample of individuals with minimal cardiovascular disease at baseline, we plan to evaluate important risk factors and predictors for SCD. In addition, we plan to evaluate the incremental predictive value of a panel of biomarkers when added to traditional risk factors. These biomarkers reflect diverse pathophysiological pathways implicated in cardiovascular disease including inflammation (C-reactive protein), neurohormonal regulation and hemodynamic stress (NT-pro BNP), cardiac injury (high sensitive cardiac troponin T), and kidney function (cystatin C). Finally, we will validate our findings from the Cardiovascular Health Study where we have identified a series of clinical risk factors and predictors for SCD.

5. Main Hypothesis/Study Questions:

We hypothesize the following:

A. The analysis of cardiac biomarkers will identify a combination that improves risk stratification for SCD beyond clinical risk factors.
B. The risk prediction model derived in the Cardiovascular Health Study, a population-based study of the elderly, will be validated in ARIC.
C. The optimal risk prediction model for SCD will be different than that for non-sudden cardiac death (non-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).

Part I: Exploratory analyses of baseline ARIC data:

A. We will start by identifying a baseline model that contains demographics, clinical parameters, and medical history. Specifically, the association between the baseline covariates listed below and SCD will be evaluated. Those variables that are associated with SCD at a p-value < 0.1 will be included in a backward stepwise elimination model. A retention criteria of $p<0.2$ will then be used to select candidate variables to be included in the multivariate Cox proportional hazards model. The specific variables of interest include the following:

Demographic and Clinical Parameters:
Age, gender, race,
Education
Smoking (current, former)
Alcohol use
Body mass index
Physical activity
Systolic blood pressure, mm Hg
Diastolic blood pressure, mm Hg
Hypertension
- BP mean (systolic and diastolic)

Diabetes
Coronary Heart Disease
Congestive Heart Failure
Stroke

Family history of cardiovascular disease
Estimated GFR (creatinine-based)

Laboratory measures:
Calcium, phosphorus, potassium, albumin, hemoglobin, LDL, HDL

Electrocardiographic measures: atrial fibrillation, left ventricular hypertrophy, QT interval (msec), left bundle branch block

B. The C-index for this ARIC-derived model using baseline variables will be calculated.

Part II: Biomarker Data (Visit 4):

Using the final model in part I, we will evaluate whether biological markers from visit 4 (CRP, BNP, Cystatin C, high-sensitivity troponin T) improve SCD risk prediction (C-statistic). Specifically:

A. Survival analyses using Cox proportional hazards modeling: Evaluate the unadjusted association between each biomarker and SCD. Biomarkers will be modeled as linear (per SD) and categorical (quartiles) variables.

B. Adjusted analyses: we will evaluate whether each biomarker is independently associated with SCD after adjustment for those variables that comprise the final model from part 1.

C. Those biomarkers that are independent risk factors for SCD will be included in the final model and the C-statistic for the model with and without biomarker data will be calculated.

D. Since the basic clinical, demographic model is nested within the biomarker model, we will evaluate whether the difference in C-statistic is statistically significant.

Part III: Validation Analyses:

Our next aim will be to validate the SCD risk factors and predictors identified from the Cardiovascular Health Study (CHS) (C-statistic 0.81) in ARIC (using baseline data). These risk factors include the following: age, African American race, male gender, diabetes, prevalent coronary heart disease, prevalent stroke, prevalent congestive heart failure, family history of cardiovascular disease, serum albumin, LDL, and estimated glomerular filtration rate.

A. Survival analyses using Cox proportional hazards modeling: We will assess the unadjusted and adjusted association between each risk factor above (baseline) and SCD in ARIC. We will adjust for the other risk factors depicted above.

B. Next, we will calculate the C-statistic for predicting SCD using the combination of these risk factors.

Part IV: Comparing prediction models for SCD and non-sudden cardiac death

In this next part, we will compare the ability of the SCD risk prediction model from above to discriminate SCD and non-SCD events. We will also compare a series of baseline risk factors and determine whether they have a stronger association for SCD compared to non-SCD. Risk factors that are disproportionately associated with SCD compared to non-SCD could have the greatest impact on risk prediction algorithms.

A. After identifying the optimal risk prediction model for SCD in CHS and ARIC as proposed above, we will assess the C-statistic of this model for predicting non-SCD in each cohort. The C-statistics for SCD and non-SCD will then be compared statistically.

B. We will next create a risk prediction model for non-SCD in ARIC and CHS. The association between the baseline covariates outlined in part I above (demographic and clinical parameters, laboratory measures, electrocardiographic measures, and biomarkers) and non-SCD will be evaluated. Those variables that are associated with non-SCD at a p-value < 0.1 will be included in a backward stepwise elimination model. A retention criteria of p<0.2 will then be used to select candidate variables to be included in the multivariate Cox proportional hazards model. Non-SCD will include deaths from coronary heart disease, myocardial infarction or hypertension.

C. Finally, we will use the method of data duplication of Lunn and McNeil[14] to compare the strength of associations of baseline risk factors with SCD and NSCD. Variables that comprise the SCD and non-SCD prediction models will be evaluated in this comparative analysis. We will stratify on type of event rather than assuming proportional hazards for event type. The procedure will use robust standard errors as recommended by Tai et al. [15]

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)?
This proposal is the product of a collaboration between investigators from both the Cardiovascular Health Study and ARIC. We have worked closely with several ARIC

investigators including Aaron Folsom, Alvaro Alonso, Christie Ballantyne, Selcuk Adabag and Suma Konety to ensure that this project is unique and does not overlap with other proposals.

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/

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.

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