ARIC Manuscript Proposal # 1514

PC Reviewed: 5/12/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Racial/ethnicity differences in sudden cardiac death among the combined cohorts of the Atherosclerosis Risk in Communities Study (ARIC) and the Cardiovascular Health Study (CHS)

b. Abbreviated Title (Length 26 characters): Race and SCD in ARIC and CHS cohorts

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

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3. Timeline: 2 years

4. Rationale:

Sudden cardiac death is an important contributor to total cardiovascular mortality with 300.000-400,000 deaths annually[1;2] There is evidence that SCD rates are higher for African Americans compared to other racial groups.[3-6] One possible explanation for this excess risk is racial differences in the prevalence of established risk factors for SCD, such as smoking, diabetes, [7;8] hypertension, [9;10]and ventricular hypertrophy [11] that are more prevalent in African Americans compared to Whites. Other possible explanations include unmeasured genetic variation and/or unmeasured environmental factors that are associated with race/ethnicity (including different distribution of dietary intake, body composition, occupational exposures, and other socioeconomic differences).[12;13] We explicitly recognize that racial differences in incidence of SCD potentially identified in this analysis cannot be solely attributed to genetic differences between African Americans and Whites.

Little information is available on the ability of traditional risk factors to explain differences in SCD between African Americans and Whites. Using the combined resources of the Atherosclerotic Risk in the Community (ARIC) Study and of the Cardiovascular Health Study (CHS), this investigation will provide data on SCD incidence in African Americans and Whites and will determine if racial differences can be explained by traditional cardiovascular risk factors. The identification of potentially modifiable risk factors as contributors to excess SCD risk in African Americans would potentially identify avenues for additional studies that could lead to prevention strategies.

5. Main Hypothesis/Study Questions:

To test these hypotheses, we propose a prospective study in the combined ARIC and CHS cohort.

The aims of this study are:

1. To estimate the incidence of SCD in African-Americans and White participants in the combined ARIC and CHS cohort;

2. To estimate the prevalence of CVD risk factors in African-Americans and White participants in the combined ARIC and CHS cohort;

3. To estimate the relative risk of SCD associated with established CVD risk factors in African-American and in Whites in the combined ARIC and CHS cohort;

4. To estimate the excess risk of SCD associated with differences in the prevalences of traditional CVD risk factors and strength of association with SCD in African-American vs. Whites.

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).

We are proposing a prospective cohort study where the primary outcome of interest is SCD. We will use the previously adjudicated SCD outcomes from the Reynolds SCD ancillary study (Ancillary Study Number 2004.03) which used a uniform definition of SCD for ARIC and CHS.,

Each parent study classified all cases of fatal CHD according to standard protocols. To identify cases of SCD in ARIC and CHS for the present study, all cases of fatal CHD and fatal MI that occurred by July 31, 2002 in CHS and December 31, 2002 in ARIC were reviewed and adjudicated by a committee of physicians. SCD was operationally

defined as a sudden pulseless condition from a cardiac origin in a previously stable individual. After review of data available from death certificates, informant interviews, physician questionnaires, coroner reports, and hospital discharge summaries, the reviewers classified each CHD death as definite sudden arrhythmic death, possible sudden arrhythmic death, definite non-sudden death, or unclassifiable. We a priori sought to exclude cases with non-arrhythmic characteristics including those with evidence of progressive hypotension or advanced congestive heart failure prior to death. We also excluded those cases with advanced dementia or terminal illness such as end stage cancer or liver disease. Each event was independently adjudicated by two investigators. If disagreement existed between the first two reviewers, a third investigator independently reviewed the event to provide final classification. As part of event review, information was systematically abstracted regarding duration of symptoms, whether the event was witnessed, other circumstances of the event, and medical co-morbidities of the patient in order to help classify whether the subject had experienced SCD. Those classified as "definite sudden arrhythmic death" were either confirmed by evidence of "instantaneous death" or in the case of unwitnessed deaths, there was descriptive information regarding the position of the body that indicated a sudden event had occurred. All suspected SCD, defined as a sudden pulseless condition from a cardiac origin in a previously stable individual, that we could not classify as "definite" were classified as "possible SCD". Cases were identified as either in or out of hospital deaths. The primary outcome of SCD described in the present study combines both definite and possible sudden arrhythmic death. For the present analysis, participants will be censored at time of loss to follow up or death if the cause of death was other than SCD. The administrative censoring date was July 31, 2002 for CHS and December 31, 2002 for ARIC, based on the study's adjudication schedules.

Variables of interest will include:

Demographics variables: Age, gender, marital status, educational attainment, health insurance and income.
Genetic variables: Distance from centroid of genomic features or representative European and African populations.
Risk factors of cardiovascular disease: Smoking status, alcohol use, physical activity, body mass index, diabetes and hypertension.
Other Co-morbidities: Chronic lung disease, chronic renal failure.
Events: Out-of-hospital sudden cardiac death (adjudicated previously in the Reynolds Ancillary Study)
Laboratory data: Total cholesterol, HDL and LDL cholesterol, triglycerides, fibrinogen, C-reactive protein and creatinine.
ECG data: QT interval and LVH
Physical exam: Systolic and diastolic blood pressure, heart rate.
Measures of atherosclerotic disease: History of myocardial infarction, previous CAB, previous PTCA, CVA and implantation of ICD.
Medications: antihypertensive, digoxin, β-blockers, aspirin, ACE inhibitors and lipid lowering drugs.

The Analytic methods will include:

Assess baseline differences between African Americans and Whites in established and suspected risk factors for SCD using t test and $\chi 2$ tests. SCD incidence rates will be determined using person-years approach, and a test of proportions will be used to assess differences in incident rates of SCD between African Americans and Whites.
The relative risk of incident SCD in African Americans vs. Whites will be determined using proportional hazard models. The first model will adjust for established non-modifiable risk factors including age, sex and family history. Subsequent models will be developed by introducing groups of potentially modifiable risk factors in sequence. The extent to which groups of covariates appear to modify the excess risk of SCD in African Americans will be assessed by calculating the percent reduction in RR (PR) associated with adjustment according to the PR=(ra-rb)/(ra-1), were ra would be the RR of SCD in African Americans vs. Whites in the base model, adjusted for age, gender and family history; rb would be the RR after additional adjustment for a group of covariates; and ra - 1 would be the excess risk of SCD in African Americans vs. Whites. [14]A competing risks model will de developed to take into account informative censoring from non-SCD events. [15] Sensitivity analyses would be restricted to definite vs. possible sudden arrhythmic death outcomes to test the robustness of the study results.

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? __X_ Yes ____ 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"?
__X__ Yes ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
__X__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)?

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* Ancillary Study Number 2004.03**)**

___ 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/

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.

Bibliography

1 Rubart M, Zipes DP. Mechanisms of sudden cardiac death. J Clin Invest 2005; 115(9):2305-2315.

2 Chugh SS, Jui J, Gunson K et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. J Am Coll Cardiol 2004; 44(6):1268-1275.

3 Thomas KL, Al-Khatib SM, Kelsey RC et al. Racial disparity in the utilization of implantable-cardioverter defibrillators among patients with prior myocardial infarction and an ejection fraction of <or=35%. Am J Cardiol 2007; 100(6):924-929.

4 Gillum RF. Sudden cardiac death in Hispanic Americans and African Americans. Am J Public Health 1997; 87(9):1461-1466.

5 Traven ND, Kuller LH, Ives DG, Rutan GH, Perper JA. Coronary heart disease mortality and sudden death among the 35-44-year age group in Allegheny County, Pennsylvania. Ann Epidemiol 1996; 6(2):130-136.

6 Burke AP, Farb A, Pestaner J et al. Traditional risk factors and the incidence of sudden coronary death with and without coronary thrombosis in blacks. Circulation 2002; 105(4):419-424.

7 Lipton RB, Liao Y, Cao G, Cooper RS, McGee D. Determinants of incident non-insulin-dependent diabetes mellitus among blacks and whites in a national sample. The NHANES I Epidemiologic Follow-up Study. Am J Epidemiol 1993; 138(10):826-839.

8 Harris MI, Flegal KM, Cowie CC et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988-1994. Diabetes Care 1998; 21(4):518-524.

9 Asher CR, Topol EJ, Moliterno DJ. Insights into the pathophysiology of atherosclerosis and prognosis of black Americans with acute coronary syndromes. Am Heart J 1999; 138(6 Pt 1):1073-1081.

10 Lee DK, Marantz PR, Devereux RB, Kligfield P, Alderman MH. Left ventricular hypertrophy in black and white hypertensives. Standard electrocardiographic criteria overestimate racial differences in prevalence. JAMA 1992; 267(24):3294-3299.

11 Arnett DK, Strogatz DS, Ephross SA, Hames CG, Tyroler HA. Greater incidence of electrocardiographic left ventricular hypertrophy in black men than in white men in Evans County, Georgia. Ethn Dis 1992; 2(1):10-17.

12 Kaufman JS, Cooper RS. Race in epidemiology: new tools, old problems. Ann Epidemiol 2008; 18(2):119-123.

13 Beckman M. The race for ancestral genetics in clinical trials. J Natl Cancer Inst 2006; 98(18):1270-1271.

14 Breslow NE. Statistical Methods in Cancer Research. 1990.

15 Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007; 26(11):2389-2430.

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