PC Reviewed: 5/10/11	**Status: <u>A</u>**	**Priority: <u>2</u>**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Can echocardiographic features predict sudden cardiac death? Pooled data analysis from ARIC and CHS

b. Abbreviated Title (Length 26 characters):
Echocardiography and Sudden Cardiac Death

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

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3.   **Timeline**:

Statistical Analysis: 3 months
Manuscript preparation: 3 months

4.   **Rationale**:
    Sudden cardiac death (SCD) is a major health issue claiming at least 250,000 lives in the U.S. on an annual basis (1,2). The unexpected nature of this devastating condition compounds the urgency of discovering methods for early detection of risk, which will lead to more effective prevention. However, the complex and dynamic nature of SCD continues to present a considerable challenge for the early identification of risk factors. The only major risk factor used for risk stratification in clinical practice is measurement of the left ventricular ejection fraction (LVEF). Severely decreased LVEF is likely to manifest late in the natural history of SCD, and may only affect a small subgroup of patients who will suffer SCD. In a prior ARIC community surveillance study, about a third of CHD deaths were sudden, occurring within an hour after the onset of symptoms, but majority of the sudden deaths (63.5%) had no prior diagnosis of CHD (3). The Ore-SUDS (Oregon Sudden Unexpected Death Study) showed women were significantly less likely than men to have a diagnosis of structural heart disease (LV dysfunction or coronary artery disease) before sudden cardiac arrest (4). This highlights the complexity of risk stratifying individuals for SCD purely based on left ventricular ejection fraction.

    ARIC and CHS cohorts provide a unique opportunity to study antecedent structural heart disease prior to SCD and to assess for any differences across demographic subgroups and communities. To date, we are not aware of any literature that has carefully examined echocardiographic features as predictors of SCD. Over a median follow up of 14.1 years in ARIC and 12.2 years in CHS, 334 whites and 164 blacks experienced sudden cardiac death (cumulative incidence rate per 1,000 person-years: 2.0 overall; 1.4 in ARIC and 4.5 in CHS; 1.8 in whites and 2.9 in blacks). Given the older age of the CHS cohort, 222 of the 498 SCD events (45%) occurred in CHS while 276 events occurred in ARIC. Of all CHD mortality adjudicated (N = 985), 40.2% were classified as definite SCD and 10.4% as possible SCD. The majority of cases of SCD occurred out of hospital (90%). Echocardiographic data is available in both cohorts: the Jackson cohort of ARIC study underwent echocardiograms during 1993 -1995 and the initial CHS cohort underwent echocardiograms from 1988 to 1989 and the second CHS cohort (African American) underwent echocardiograms during 1994 - 1995.

    Prior data from CHS has shown increased left ventricular mass to be associated with a higher risk of mortality even after adjusting for the traditional cardiac risk factors (9) and increasing aortic root dimensions to be a modest predictor of CVD mortality (HR 1.3-1.6 per cm of aortic root) (10). In the Jackson cohort of ARIC, left ventricular mass (in men) (11), presence of mitral annular calcification (12) have predicted an increased risk of coronary heart disease (fatal and hospitalized MI).

In this proposal we will evaluate the echocardiographic features in participants from the Jackson cohort and CHS cohort who died of sudden cardiac death and compare to participants who are alive controlling for known cardiovascular risk factors and in particular, will focus on stratified analysis by gender.

5.   Main Hypothesis/Study Questions:

1. We hypothesize that participants with impaired LV systolic function (EF <50%) will have increased risk of sudden cardiac death compared to participants with normal LV systolic function.
2. We hypothesize that compared to men; more women who died of sudden cardiac death will have preserved LVEF.
3. The prevalence of left ventricular dilatation, aortic root dilatation, left ventricular hypertrophy and left atrial dilatation will be higher in participants who died of sudden cardiac death.

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 population
The ARIC study and CHS are both population-based prospective cohort studies of cardiovascular disease. The ARIC Study included 15,792 persons aged 45–64 years at baseline (1987–89), randomly chosen from four US communities (Forsyth County, North Carolina; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, Maryland) (5). ARIC cohort members have completed four clinic examinations, conducted approximately three years apart between 1987 and 1998. During the third study visit (1993-1995), participants at the Jackson, MS, site underwent echocardiographic examination (6). The Jackson, MS, field center recruited only African Americans. CHS included 5,888 participants > 65 years of age identified from four U.S. communities (Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania) using Medicare eligibility lists (7). The initial CHS cohort (n=5201) underwent echocardiograms from 1988 to 1989 and for the second cohort (African American, n=687), echocardiography was performed in 1994 to 1995, 2 years after their entry into the study (8). We will study the entire CHS cohort (n=5888) and the Jackson Cohort of ARIC (n=2445).

Exclusion criteria: Participants with missing echocardiographic data

Predictor variables:
i. Left ventricular internal dimensions: end-diastolic and end-systolic
ii. Left ventricular ejection fraction
iii. Left ventricular mass
iv. Type of left ventricular hypertrophy: eccentric vs. concentric
v. Mitral annular calcification

vi. Aortic root dimension
vii. Aortic regurgitation and mitral regurgitation
viii. Aortic stenosis and sclerosis

Outcome variable:
In this combined ARIC and CHS cohort, all cases of fatal CHD (definite MI, definite fatal CHD, or possible fatal CHD, in and out of hospital) 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 defined as a sudden pulseless condition from a cardiac origin in a previously stable individual. After review of available data, cases were classified as definite sudden arrhythmic death, possible arrhythmic death, not sudden arrhythmic death, or unclassifiable. SCD was defined as the first 2 categories. Cases were identified as either in or out of hospital deaths. The primary outcome of SCD described in the present study used only definite SCD cases in the analyses. Also, for the present analyses, participants were censored at time of loss to follow up or death if the cause of death was other than SCD. Over a median follow up of 14.1 years in ARIC and 12.2 years in CHS, 334 whites and 164 blacks experienced sudden cardiac death.

Covariates (from the time of the echocardiographic exam):
Age, gender, race, study center, education level, heart rate, smoking status (current, former/never), body mass index, hypertension (SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg or antihypertensive medication use or physician diagnosis of hypertension, diabetes, hypercholesterolemia, history of MI, coronary heart disease, heart failure, and use of β-blockers and anti-arrhythmic drugs.

Statistical analysis
Data from the CHS participants who underwent echocardiogram in year 2 (n = 5176 from the original cohort) and in year 7 (n = 507 from the African American cohort) and African American subjects (n=2,445) from the Jackson ARIC cohort will be pooled together and analyzed. Data collection from echocardiography in the two studies was similar. Data variables that are available in both studies will be included in this present analysis.

We will provide descriptive statistics on participants in the analysis who did and did not sustain SCD. We will estimate associations between measures of LV structure and function and subsequent SCD using Cox proportional hazard models first adjusting for age and sex and then also for cardiovascular risk factors, cardiac medications and comorbid conditions. Effect modification would be examined by age, sex, race, renal disease before the echocardiogram. We would repeat these analyses screening other echocardiography variables for their association with SCD after the echocardiogram. These variables will include left atrial size and function, valvular regurgitation, valvular stenosis, aortic root size.

Summary/conclusion
We will seek associations between echocardiographic data and incident sudden cardiac death. This is particularly important as a significant proportion of sudden deaths still occur in the individuals without a history of coronary artery disease. If echocardiographic

features are predictive of sudden death, then the implications about the possible prevention of SCD will be substantial.

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

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?   ____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)?
Dr. Fox (investigator from the Jackson Heart Study) is a member of the writing group.

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

__ 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.

References

1. 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;44:1268 –75.

2. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115:e69 –171.

3. Ni H, Coady S, Rosamond W, Folsom AR, Chambless L, Russell SD, Sorlie PD. Trends from 1987 to 2004 in sudden death due to Coronary heart disease: The Atherosclerosis Risk In Communities (ARIC) study. Am Heart J 2009;157:46-52.

4. Chugh SS, Uy-Evanado, A, Teodorescu, C, Reinier, K, Mariani, R, Gunson, K, Jui, J. Women Have a Lower Prevalence of Structural Heart Disease as a Precursor to Sudden Cardiac Arrest The Ore-SUDS (Oregon Sudden Unexpected Death Study). J Am Coll Cardiol 2009; 54:2006–11.

5. The atherosclerosis risk in communities (ARIC) study: Design and objectives. the ARIC investigators.(1989). *American Journal of Epidemiology, 129*(4), 687-702.

6. Sempos CT, Bild DE, Manolio TA, et al: Overview of the Jackson Heart Study: A study of cardiovascular diseases in African American men and women. Am J Med Sci 1999;317:142–146.

7. Fried, L. P., Borhani, N. O., Enright, P., Furberg, C. D., Gardin, J. M., Kronmal, R. A., et al. (1991). The cardiovascular health study: Design and rationale. *Annals of Epidemiology, 1*(3), 263-276.

8. Gardin, J. M., Wong, N. D., Bommer, W., Klopfenstein, H. S., Smith, V. E., Tabatznik, B., Siscovick, D., Lobodzinski, S., Anton-Culver, H., and Manolio, T. A. *Echocardiographic design of a multicenter investigation of free-living elderly subjects: the Cardiovascular Health Study*. J.Am.Soc.Echocardiogr.1992; (5), 63-72.

9. Gardin, J. M., McClelland, R., Kitzman, D., Lima, J. A., Bommer, W., Klopfenstein, H. S., et al. (2001). M-mode echocardiographic predictors of six- to seven-year incidence

of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (the cardiovascular health study). *The American Journal of Cardiology, 87*(9), 1051-1057.

10. Gardin, J., Arnold, A., Polak, J., Jackson, S., Smith, V., & Gottdiener, J. (2006). Usefulness of aortic root dimension in persons > or = 65 years of age in predicting heart failure, stroke, cardiovascular mortality, all-cause mortality and acute myocardial infarction (from the cardiovascular health study). *The American Journal of Cardiology, 97*(2), 270-275.

11. Taylor, H., Penman, A., Han, H., Dele-Michael, A., Skelton, T., Fox, E., et al. (2007). Left ventricular architecture and survival in african-americans free of coronary heart disease (from the atherosclerosis risk in communities [ARIC] study). *The American Journal of Cardiology, 99*(10), 1413-1420.

12. Fox, E., Harkins, D., Taylor, H., McMullan, M., Han, H., Samdarshi, T., et al. (2004). Epidemiology of mitral annular calcification and its predictive value for coronary events in african americans: The jackson cohort of the atherosclerotic risk in communities study. *American Heart Journal, 148*(6), 979-984.