

ARIC Manuscript Proposal # 1214

PC Reviewed: 1 / 9 /06
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title:

Diabetes, inflammation and sudden coronary death in the ARIC study cohort

b. Abbreviated Title (Length 26 characters):

Diabetes and sudden death

2. Writing Group:

Writing group members (in alphabetical order): David Couper, Aaron Folsom, James Pankow, Ronald Prineas, Thomas Rea, Wayne Rosamond, David Siscovick, Nona Sotoodehnia

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

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3. Timeline:

Data analysis to begin upon approval of proposal, with March 2007 as the completion date. Draft of manuscript: June 2007.

4. Rationale:

Traditional cardiovascular risk factors, although associated with sudden cardiac death in persons without any evidence of prior cardiovascular disease, lack predictive power necessary for prevention (1). The consistently high proportion of total CHD mortality attributed to sudden cardiac deaths (2) necessitates development of studies aimed at identifying specific risk factors and characterization of populations at elevated risk.

Recent data from the Framingham study suggest an increase in the prevalence of Type 2 diabetes by decade of cardiac death from 1950 until 1999, with a greater increase in prevalence of diabetes observed among victims of sudden cardiac death relative to that of victims of coronary heart disease death preceded by a diagnosis of CHD or CHF (3). In the present study we propose to use the recently validated incidence of sudden cardiac death in the ARIC and CHS cohorts to address a possible etiologic basis for this suggested difference in trends.

In several studies, Type 2 diabetes mellitus, a clinical condition with an established inflammatory basis (4), has been found to be associated with a higher relative risk of sudden cardiac death as compared to non-sudden cardiac death (5-7). Although those studies highlighted the possibility of a more specific association of diabetes with sudden cardiac death, limitations inherent in study design necessitate further studies that would confirm, or refute, those observations. Specifically: the case-control design of the study by Jouven et al. (7) did not allow for a prospective analysis of diabetes as a risk factor and in the Paris Prospective Study I (5, 6) the number of cases of diabetes associated with sudden cardiac death, or with fatal myocardial infarction (the comparison category) was very small. Furthermore, given an observed gender-related difference in the association of diabetes with sudden cardiac death, the all-male design of the latter study did not allow for a comprehensive analysis of the association.

In a study based on the Physicians Health Study, Albert et al. (8) examined possible association of C-reactive protein (CRP) and the incidence of sudden cardiac death. Even though this was a small nested case control study, the positive association of CRP with incidence of sudden cardiac death was statistically significant. To our knowledge, this study is the only one that addresses possible associations of inflammation and sudden cardiac death; however the small number of cases, lack of comprehensive adjustment for obesity-related characteristics, and smoking status, as well as a selective study population (men only, study participants treated with aspirin) preclude its representativeness.

The premise of this proposal is that stratification of risk of sudden cardiac death by levels of inflammation may potentially allow for better identification of at-risk populations. A recently published study by Reinier et al. (9), indicates that low neighborhood socioeconomic status may be associated with higher incidence of sudden cardiac death. Data from studies examining socioeconomic status and incidence of Type 2 diabetes (10, 11) suggest an association of lower social position and related health

behaviors and exposures with development of type 2 diabetes. Those studies indicate a need for further, more detailed analyses of sudden cardiac death in the context of inflammation and associated clinical conditions, such as type 2 diabetes.

In this study we would like to use recently validated data from the ARIC and CHS study cohorts concerning incident cases of sudden cardiac death to examine the association of baseline and incident type 2 diabetes with incidence of sudden cardiac death. In addition, we will assess the effect of baseline inflammatory burden, as determined by baseline levels of fibrinogen and white blood cell count, on the found association as well as independently. Association of fibrinogen and white blood cell count with coronary heart disease events has been validated in numerous long-term prospective studies (12). Association of those measures of acute phase reaction specifically with incidence of sudden cardiac death has not been established.

References:

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3. Fox CS, Evans JC, Larson MG, et al. Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999. *Circulation* 2004;110:522-527.
4. Sjöholm A, Nystrom T. Inflammation and the etiology of type 2 diabetes. *Diabetes/Metabolism Research and Review* 2006;22:4-10.
5. Balkau B, Jouven X, Ducimetiere P, et al. Diabetes as a risk factor for sudden death. *The Lancet* 1999;354:1968-1969.
6. Jouven X, Desnos M, Guerto C, et al. Predicting sudden death in the population, the Paris Prospective Study I. *Circulation* 1999;99:1978-1983.
7. Jouven X, Lemaitre RN, Rea TD, et al. Diabetes, glucose level, and the risk of sudden cardiac death. *European Heart Journal* 2005;26:2142-2147.
8. Albert CM, Ma J, Rifai N, et al. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation* 2002;105:2595-2599.
9. Reinier K, Stecker EC, Vickers C, et al. Incidence of sudden cardiac arrest is higher in areas of low socioeconomic status: A prospective two year study in a large United States community. *Resuscitation* 2006;70:186-192.
10. Jotkowitz AB, Rabinowitz G, Segal AR, et al. Do patients with diabetes and low socioeconomic status receive less care and have worse outcomes? A national study. *The American Journal of Medicine* 2006;119:665-669.
11. Kumari M, Head J, Marmot M. Prospective study of social and other risk factors in incidence of type 2 diabetes in the Whitehall II Study. *Archives of Internal Medicine* 2004;164:1873-1880.

12. Danesh J, Collins R, Appleby P, et al. Association of Fibrinogen, C-reactive Protein, Albumin, or Leukocyte Count With Coronary Heart Disease: Meta-analyses of Prospective Studies. JAMA 1998;279:1477-1482.

5. Main Hypothesis/Study Questions:

1. Type 2 diabetes mellitus is associated with an increased relative risk of sudden cardiac death. This association is greater for sudden cardiac death as compared to cardiac death related to known cardiac causes.
2. The association of baseline Type 2 diabetes with incidence of sudden cardiac death can be explained partially by elevated levels of markers of inflammation (fibrinogen, white blood cell count).
3. Elevated levels of fibrinogen and white blood cell count are associated with an increased risk 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).

1. Study population: Data from the ARIC study cohort will be used in this analysis. We performed a power analysis and found that the number of incident sudden death cases in the ARIC cohort (321) is sufficient to detect a hazard ratio of 1.6 with a power of 90% and 95% confidence.
2. Definition of sudden cardiac death: sudden cardiac death will be defined as proposed by Reynolds Project (MS#1086r) to be “death adjudicated by a physician panel to be a sudden, pulseless condition without a known non-cardiac cause, or death certificate codes indicating death due to underlying heart disease that occurs outside the hospital or in the emergency department”.
3. Baseline variables: gender, race, BMI, waist-hip-ratio, fibrinogen, white blood cell count, albumin, diabetes status, fasting glucose levels, smoking status (current, former, never), pack-years of cigarettes, physical exercise, individual measures of socioeconomic status (income level, education), diabetes medications, anti-inflammatory medications.
4. Type 2 diabetes status past baseline will be defined on the basis of information obtained at times determined by the dates of follow-up visits of the ARIC study. Analysis: Multivariate Cox proportional hazard regression with time-varying covariates. Diabetes exposure will include cases of type 2 diabetes diagnosed at baseline and at follow-up visits.

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 ICTDER02 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 ICTDER02 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
 No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 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.csc.unc.edu/ARIC/search.php>

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)?

MS#1086r: Epidemiologic Implications of the Cardiac Arrest Case Definition

This manuscript outlines a proposal to identify and validate sudden cardiac death cases in the ARIC and CHS cohorts and create a common cohort including data from both studies. As such it constitutes the basis for our proposed study. The scope of MS#1086 is very broad and it does include analysis of the association of cardiovascular risk factors with incidence of sudden cardiac death. Its emphasis though is on the definition of sudden cardiac death and implications thereof. The focus of our proposal is diabetes and its significance with respect to development of sudden cardiac death. We would use the definition of SCD developed as part of MS#1086 and explore in detail the effect of prevalent and incident diabetes on the incidence of sudden cardiac death.

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

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list 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.csc.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.**