

ARIC Manuscript Proposal # 1875

PC Reviewed: 12/13/11
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title:

Does the Metabolic Syndrome Add Prognostic Information Beyond Traditional Risk Factors in the Prediction of Sudden Cardiac Death? Insights from the Atherosclerosis in Communities (ARIC) Study

b. Abbreviated Title:

Sudden Cardiac Death in Metabolic Syndrome

2. Writing Group:

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

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3. Timeline:

We aim submit to the Journal of the American Medical Association in November of 2012.

4. Rationale:

The metabolic syndrome, a highly prevalent clustering of cardiovascular disease risk factors [1], was first proposed as a unique pathophysiological condition in 1967[2]. Since the publication of Reaven's seminal Banting award lecture in 1988[3], a large body of evidence linking the metabolic syndrome to cardiovascular disease and its sequelae has accumulated. However, it was not until the past 9 years that controversy regarding its value as a marker of cardiovascular disease emerged.

A study in non-diabetic American Indians first raised doubt regarding the utility of the metabolic syndrome as a predictor of cardiovascular disease in 2003. Based on 2,283 subjects free of cardiovascular disease followed for an average of 7.6 years, the risk of cardiovascular disease did not increase as a function of the presence or absence of metabolic syndrome[4]. ARIC study investigators came to a similar conclusion in 2005. Based on 12, 089 black and white individuals followed for an average of 11 years, receiver operator curves suggested that the metabolic syndrome was no better than the Framingham Risk Score in predicting cardiovascular risk[5]. Studies from Britain and Finland had comparable findings[6-8].

In contrast, a significant number of studies support the notion that the metabolic syndrome predicts cardiovascular events independent of traditional cardiovascular risk factors. The Kuopio Ischaemic Heart Disease Risk Factor Study followed 1, 209 Finnish men for an average of 11.4 years. After adjustment for traditional risk factors, men with the metabolic syndrome were at a higher risk of dying from cardiovascular disease or other causes[9]. Similarly, in the West of Scotland Coronary Prevention Study 6,477 men were followed for an average of 4.9 years. The metabolic syndrome was predictive of coronary heart disease in multivariate modeling even when established risk factors were incorporated[10]. These findings have been replicated in hypertensive patients[11]. Further, using high thresholds for exclusion, a meta-analysis showed an increased risk of cardiovascular disease or death in patients with the metabolic syndrome after controlling for its component risk factors[12].

Cardiovascular disease and lethal ventricular arrhythmias are closely related. In fact, half of cardiovascular deaths have been estimated to be sudden[13, 14]. Unfortunately, rates of SCD have not declined as quickly as those of other modes of cardiovascular death[15,

16]. In spite of advances in the prevention and treatment of coronary disease and the dissemination of implantable cardioverter-defibrillators, the proportion of cardiovascular deaths that are sudden is increasing. Interestingly, the time course of the rise in proportion of SCD resembles that seen in the prevalence of the metabolic syndrome. We hypothesize that these unfavorable trends are interrelated and thus the metabolic syndrome adds prognostic information beyond traditional cardiovascular risk factors in the prediction of SCD.

Although a large number of studies investigating the cardiovascular risk associated with the metabolic syndrome have been published, only a single study has examined the association between the metabolic syndrome and SCD per se. In the Paris Prospective Study I, 6,678 men free of coronary heart disease at baseline were followed for an average of 21.2 years. HDL cholesterol was unobtainable, and sagittal abdominal diameter was used as a surrogate for waist circumference. After adjustment for other cardiovascular disease risk factors, the metabolic syndrome at baseline increased the risk of SCD by 68% [17].

The Atherosclerosis Risk in Communities study is uniquely suited to address our hypothesis. Due to its large size, longitudinal follow-up of more than twenty years, multiple participating sites, and the fact that it is population-based, it has ample power and generalizability. Although associations between the metabolic syndrome and other outcomes have been examined in the ARIC study [5, 18, 19], its association with SCD has not been considered. Further, data are more granular and more complete than that seen in many prior studies. In contrast to the Paris Prospective Study I, for example, HDL and waist circumference are available for analysis.

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2. Avogaro, P., et al., *Associazione di Iperlipidemia, Diabete Mellito, i Obesita de Medio Grado*. Acto Diabetol Lat, 1967. **4**: p. 36-41.
3. Reaven, G.M., *Role of Insulin Resistance in Human Disease*. Diabetes, 1988. **37**: p. 1595-1607.
4. Resnick, H.E., et al., *Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease in nondiabetic american indians: the Strong Heart Study*. Diabetes Care, 2003. **26**(3): p. 861-7.
5. McNeill, A.M., et al., *The Metabolic Syndrome and 11-Year Risk of Incident Cardiovascular Disease in the Atherosclerosis Risk in Communities Study*. Diabetes Care, 2005. **28**: p. 385-390.
6. Wannamethee, S.G., et al., *Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus*. Arch Intern Med, 2005. **165**(22): p. 2644-50.
7. Wang, J., et al., *The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns*. Eur Heart J, 2007. **28**(7): p. 857-64.
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9. Lakka, H.M., et al., *The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men*. JAMA, 2002. **288**(21): p. 2709-16.

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10. Sattar, N., et al., *Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study*. *Circulation*, 2003. **108**(4): p. 414-9.
11. Schillaci, G., et al., *Prognostic value of the metabolic syndrome in essential hypertension*. *J Am Coll Cardiol*, 2004. **43**(10): p. 1817-22.
12. Gami, A.S., et al., *Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies*. *J Am Coll Cardiol*, 2007. **49**(4): p. 403-14.
13. Myerburg, R.J., K.M. Kessler, and A. Castellanos, *Sudden Cardiac Death: Epidemiology, Transient Risk, and Intervention Assessment*. *Ann Intern Med*, 1993. **119**: p. 1187-1197.
14. Kong, M.H., et al., *Systematic review of the incidence of sudden cardiac death in the United States*. *J Am Coll Cardiol*, 2011. **57**(7): p. 794-801.
15. Zheng, Z.J., et al., *Sudden cardiac death in the United States, 1989 to 1998*. *Circulation*, 2001. **104**(18): p. 2158-63.
16. Fox, C.S., et al., *Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999: the Framingham Heart Study*. *Circulation*, 2004. **110**(5): p. 522-7.
17. Empana, J.P., et al., *Contribution of the metabolic syndrome to sudden death risk in asymptomatic men: the Paris Prospective Study I*. *Eur Heart J*, 2007. **28**(9): p. 1149-54.
18. Burchfiel, C.M., et al., *Metabolic syndrome and echocardiographic left ventricular mass in blacks: the Atherosclerosis Risk in Communities (ARIC) Study*. *Circulation*, 2005. **112**(6): p. 819-27.
19. Chamberlain, A.M., et al., *Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the Atherosclerosis Risk in Communities (ARIC) Study*. *Am Heart J*, 2010. **159**(5): p. 850-6.

5. Hypothesis/Study Aims:

Hypothesis

We hypothesize that the metabolic syndrome at baseline (a) increases the risk of SCD and (b) adds prognostic information beyond traditional risk factors for cardiovascular disease.

Study Aims

1. To compare the incidence of SCD in patients with and without the metabolic syndrome.
2. To examine whether the metabolic syndrome adds prognostic information beyond traditional cardiovascular disease risk factors for 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).

Exclusion Criteria

We will exclude patients with prevalent cardiovascular disease (defined as self-reported myocardial infarction, heart or vascular surgery, coronary bypass, coronary angioplasty, or ECG evidence of myocardial infarction). We will also exclude patients with missing

data on important covariates such as those required to identify subjects with the metabolic syndrome.

Identification of the Metabolic Syndrome

In the primary analysis, we will use a harmonized definition proposed by the International Diabetes Federation Task Force on Epidemiology and Prevention; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity. The metabolic syndrome will be considered present if 3 or more of the following individual components are present: waist circumference ≥ 35 inches (88 cm) for women or ≥ 40 inches (102 cm) for men; fasting blood sugar ≥ 100 mg/dL (5.5 mmol/L) or treatment with hypoglycemic agents or insulin; systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mm Hg or antihypertensive drug treatment; serum triglycerides ≥ 150 mg/dL (1.7 mmol/L) or treatment for hypertriglyceridemia (with niacin or fibrates); and HDL-C < 40 mg/dL (1.0 mmol/L) in men or < 50 mg/dL (1.3 mmol/L) in women.

To ascertain the effect of the various definitions of the metabolic syndrome, sensitivity analyses will be performed using criteria proposed by the World Health Organization, the National Cholesterol Education Program Adult Treatment Panel III, and the International Diabetes Federation Epidemiology Task Force Consensus group.

Outcomes

SCD has been carefully adjudicated using two definitions. First, it has been defined as witnessed death within 1 hour of acute cardiac symptoms. Second, it has been defined as a sudden pulseless condition of cardiac origin in a previously stable individual. This definition is available only through 2002. We will use the former definition of SCD in the primary analysis and the latter definition in sensitivity analyses.

Analyses

Baseline characteristics of patients with the metabolic syndrome and those without the metabolic syndrome will be compared using the Wilcoxon rank sum test for continuous variables and the Chi square test for categorical variables. The incidence rates will be computed and the risk of SCD will be estimated for each group. Time to SCD for each group will be displayed using Kaplan-Meier curves and will be compared using the log rank test. Cox proportional hazards models will be used to examine factors associated with SCD. Models will be constructed with and without the components of the metabolic syndrome. Potential covariates to include in the regression model are age, sex, race, blood pressure, high density lipoprotein level, serum triglycerides, serum glucose, serum electrolytes, waist circumference, BMI, diabetes status, chronic renal insufficiency, left ventricular hypertrophy, resting heart rate, atrial fibrillation, incident heart failure, incident myocardial infarction, incident stroke, family history of premature coronary disease, angina or claudication, level of physical activity, field center, presence of major ECG abnormality on Minnesota code, and smoking status. The following cardiac medications will also be included: selective and non-selective β -blockers, angiotensin-converting enzyme inhibitors, digitalis, and antiarrhythmic drugs. To account for the

development of the metabolic syndrome during the course of the study, the measurements required to define metabolic syndrome will be obtained from follow-up visits and the metabolic syndrome will be included in the models as a time-dependent covariate. To account for lipid-lowering therapy initiated during follow-up, we will include the variable in the models as a time-dependent covariate. The analyses will be repeated using a landmark analysis. That is, Cox's proportional hazards models will be constructed at different time points to identify the risk factors for sudden cardiac death as a function of time after development of metabolic syndrome. Sensitivity analyses will also be performed using alternative definitions of the metabolic syndrome and SCD mentioned previously. The C-index will be used to compare the predictive value of the metabolic syndrome with that of traditional risk factors. The net reclassification improvement will also be computed.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes
 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
 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.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 1775. Risk of Sudden Cardiac Death in Relation to Obesity in the General Population

2. Writing Group:

Writing group members: Selcuk Adabag, Lin Y. Chen, Alvaro Alonso, Suma Konety, Aaron R. Folsom, Nona Sotoodehnia, David Siskovick, Jorge Kizer, Kenneth Mukamal, Michael Rosenberg.

MS 1389 Metabolic Syndrome and Risk of Incident Atrial Fibrillation among Whites and Blacks in the Atherosclerosis Risk in Communities (ARIC) Study

2. Writing Group:

Writing group members: Alanna Chamberlain, Sunil K. Agarwal, Marietta Ambrose, Aaron Folsom, Elsayed Z. Soliman, Alvaro Alonso

MS 1214 Diabetes, inflammation and sudden coronary death in the ARIC study cohort

2. Writing Group:

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

MS 1151 “Comparison of The Prognostic Significance of The Frontal Plane QRS/T Axis Angle, Spatial QRS/T Angle, and ST-T Abnormalities For Prediction Of Coronary Heart Disease Outcome and Total Mortality in the Atherosclerosis Risk In Communities Study (ARIC)

2. Writing Group (list individual with lead responsibility first):

Zhang ZM, Soliman EZ, Prineas RJ, Rautaharju PM

MS 979 Factors of the metabolic syndrome and incidence of coronary heart disease, stroke and type 2 diabetes

2. Writing Group (list individual with lead responsibility first):

Lead: Weihong Tang

Writing group members: James Pankow, Sherita Hill Golden, Maria Inês Schmidt, Christie

M. Ballantyne, Heejung Bang, a UNC representative, a Jackson center representative

MS 832 Prediction of subclinical atherosclerosis, incident CHD, and all-cause mortality using recently published definitions of the metabolic syndrome

2. Writing Group (list individual with lead responsibility first):

Lead: Annie McNeill, MPH

Writing group members: Wayne Rosamond, Gerardo Heiss, Bruce Duncan

MS 831 Associations of new definitions of the metabolic syndrome with cardiovascular disease and atherosclerosis

2. Writing Group (list individual with lead responsibility first):

Lead: Annie McNeill, MPH

Writing group members: Wayne Rosamond, Gerardo Heiss, Sherita Golden, Bruce

Duncan, Maria Schmidt, Christie Ballantyne, Honey Holman, Cynthia Girman

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

Ancillary study 2004.03

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.