ARIC Manuscript Proposal # 1931

PC Reviewed: 4/17/12  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Fish-Derived N-3 Polyunsaturated Fatty Acids and electrocardiographic repolarization abnormalities predictive of Sudden Cardiac Death In The Atherosclerosis Risk In Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): N-3 PUFAs and ECG variables

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

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3. Timeline:

   Manuscript Preparation: July 2012 – October 2012
   Manuscript Revision: November 2012
   Manuscript Submission: December 2012
4. Rationale:

Individuals with who regularly consume fish high in omega-3 fatty acids have been shown to have lower incidence of sudden cardiac death (SCD) versus those with who consume no fish or lower amounts of fish,\textsuperscript{1,2} but the exact mechanism(s) underlying this association are unconfirmed. Some evidence suggests that fish-derived oils fatty acids could have anti-arrhythmic effects, thus reducing SCD risk. Specifically, fish-derived omega-3 polyunsaturated fatty acids (PUFAs) may inhibit the fast, voltage-dependent sodium current and the L-type calcium currents\textsuperscript{3,4} that allow pre-SCD arrhythmias to be sustained.\textsuperscript{1} Therefore, investigating potential associations between the fish-derived PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and electrocardiogram (ECG) variables associated with pre-SCD arrhythmias may elucidate the mechanism underlying the association between fish consumption and reduced SCD.

The two ECG variables consistently associated with a higher risk of SCD are long QT interval and J point elevation\textsuperscript{5-8} and both are important markers of abnormal ventricular repolarization. The QT interval represents electrical depolarization and repolarization of the left and right ventricles and a prolonged QT interval is associated with SCD.\textsuperscript{5,6} Additionally, early repolarization characterized by an elevation of the QRS–ST junction (J point) has been associated with idiopathic ventricular fibrillation.\textsuperscript{7,8}

Intake of fish-derived omega-3 PUFAs have been shown to be associated with favorable QT intervals in Greek adults\textsuperscript{9} and Americans aged >65 years.\textsuperscript{10} Studies investigating the association between DHA, EPA, and J point elevation have not been conducted.

Although fish-derived omega-3 PUFAs are inversely associated with SCD, and long QT interval and J point elevation are positively associated with SCD, further details regarding the association between fish-derived omega-3 fatty acids, QT interval, and J point elevation in American middle-aged populations may help elucidate the relationship between fish consumption and reduction of SCD and the underlying mechanisms.

5. Main Hypothesis/Study Questions:

Is consumption of the fish-derived n-3 PUFAs DHA and EPA associated with heart rate corrected QT interval (QTc) prolongation or J point elevation in ARIC participants?

We hypothesize that lower dietary intake of fish, DHA, and EPA and serum levels of fish derived n-3 fatty acids DHA and EPA (biomarkers of intake- measured in a subset) will be associated with longer QTc interval and presence of J point elevation.

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 Design: We propose to conduct a longitudinal analysis of the ARIC study excluding all participants with a history of cardiovascular disease (CHD, heart failure, stroke) at baseline.
**Study Population:** All ARIC participants who meet the inclusion criteria. Inclusion criteria will be applied at each visit and subjects excluded as necessary. Inclusion criteria: no history of CVD, not taking anti-arrhythmic medications, with a QRS interval < 120 ms as those with >=120 ms have major conduction defects that make the interpretation of primary repolarization abnormalities inappropriate.

**Exposures:** Exposure to fish-derived n-3 PUFAs was assessed three ways in ARIC:

1. Oily fish, other (non-oily) fish, shellfish, and canned tuna intake (in servings/week) was measured with a food frequency questionnaire (FFQ) at visits 1 and 3
   a. We will consider total fish and oily fish with sensitivity analyses for other types of fish.
   b. Intake will be categorized into servings/week (0, <1, 1 to <2, and 2+).
2. Daily intake of DHA and EPA (in g/day) was derived from the FFQ
   a. We will consider DHA only, EPA only, and DHA+EPA
   b. Fatty acids will be categorized into quartiles
      1. Quartiles will be based on overall intake but sensitivity analyses will be performed using sex-specific quartiles.
3. In the Minnesota field center only, plasma fatty acid concentration was measured in stored samples from the baseline visit as percent of total fatty acids
   a. We will consider DHA only, EPA only, and DHA+EPA
   b. Fatty acids will be categorized into quartiles

**Outcomes:** ECGs were obtained at all four visits. Outcomes are as follows:

- **Heart rate corrected QT (QTc) calculated according to the current recommendations of the American Heart Association (AHA), American College of Cardiology (ACC) and Heart Rhythm Society (HRS) for the Standardization and Interpretation of the Electrocardiogram (ref), as follows:**
  a. Automatically measured uncorrected QT interval with adjustment for heart rate in the models
  b. Using common linear models for calculation of QTc such as Framingham \[ QT_{Fram} = QT + 154 \left (1 - \frac{60}{\text{heart rate}} \right) \] \(^{11, 12} \) or Hodges \[ QT_{Hod} = QT + 1.75 \left (\text{HR} - 60 \right) \] \(^{13} \)
  c. To provide comparability to other studies, we will also use the traditional Bazett QT correction, despite the explicit recommendation of not using it because of under or over correction in above average heart rates.
  d. Prolonged QT will be defined as values of 460 ms or longer in women and 450 ms or longer in men \(^{11} \)

2. **J-point elevation**
   a. As a continuous value as measured by the offset of the QRS complex in each of the 12 ECG leads
   b. **STJ as a categorical variable defined as elevation of greater than 100 micorvolt (1 mm).**
      a. Elevation in at least two of II, III, aVF, OR
      b. Elevation in at least two of I, aVL, V5 and V6 OR
c. Elevation of (V1 and V2) OR (V2 and V3) OR (V3 and V4) OR (V4 and V5) OR (V5 and V6)

- STJ as a categorical variable defined as elevation of greater than 200 microvolt (2 mm).
  a. Elevation in at least two of II, III, aVF, OR
  b. Elevation in at least two of I, aVL, V5 and V6 OR
  c. Elevation of (V1 and V2) OR (V2 and V3) OR (V3 and V4) OR (V4 and V5) OR (V5 and V6)

Confounders: In our analysis we will consider the following variables as potential confounders: BMI, weight gain, physical activity, alcohol intake, intake of cereal fiber, saturated fats and trans fats, total calorie intake, smoking, age, race, educational level, sex, and study center. Confounder values will be measured during the same visit as exposure values.

Potential Modifiers: Race, sex, and BMI are potential effect modifiers and will be evaluated as such.

Analyses:

- Continuous outcomes will use mixed models regression with exposures at visit 1 and updated with a cumulative average value at visit 3 and outcomes updated at each visit:
  o Visit 1 diet, Visit 1 ECG
  o Visit 1 diet, Visit 2 ECG
  o Average(Visit 3, Visit 1) diet, Visit 3 ECG
  o Average(Visit 3, Visit 1) diet, Visit 4 ECG

- Dichotomous outcomes will use logistic regression (GENMOD) and GEE to model a maximum of four “observations” for each subject
  o Visit 1 diet, Visit 1 ECG
  o Visit 1 diet, Visit 2 ECG
  o Average(Visit 3, Visit 1) diet, Visit 3 ECG
  o Average(Visit 3, Visit 1) diet, Visit 4 ECG

- Missing Data: If dietary data are available at Visit 1 but missing at Visit 3 the Visit 1 value will be carried forward.

Methodologic Issues: There are at least three limitations related to our study design:

1. Measurement error: fish/n3 PUFA intake will be assessed using a FFQ. Even though this questionnaire has been validated, measurement error is certain to exist.
2. As preparation technique is not available we will be unable to differential between fried fish and other types of fish.
3. Data are limited on fish oil supplements. Although fish oil supplements were not widely used in the late 1980’s early 1990’s, at baseline there were n=108 fish oil supplement
users in the MN cohort (2.7%). Additionally, a vitamin survey (including fish oil supplements) was conducted during visit 3. Sensitivity analyses will be performed to determine if inclusion or exclusion of these subjects affect the measures of association.

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)?

We found two related manuscript:
MS 1506 Gronroos – n-3 and AF in ARIC
MS 1601 Olson J-point Elevation Prognosis

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/

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: