

## ARIC Manuscript Proposal # 1506

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**1.a. Full Title:** Plasma n-3 fatty acids, fish intake, and incidence of Atrial Fibrillation in the Atherosclerosis Risk in Communities (ARIC) Study

**b. Abbreviated Title (Length 26 characters):** n-3 and AF in ARIC

**2. Writing Group:**

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

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**3. Timeline:**

Statistical Analysis:	April 2009 – July 2009
Manuscript Preparation:	August 2009 – November 2009
Manuscript Revision:	December 2009
Manuscript Submission:	December 2009

#### 4. Rationale:

Atrial fibrillation (AF) is the most common sustained cardiac dysrhythmia in clinical practice, and is associated with increased stroke and cardiovascular morbidity and mortality [1]. AF currently affects more than 2.2 million Americans [2], and the lifetime risk for development of AF in men and women over 40 years of age is 1 in 4 [1].

Consumption of fish with high levels of n-3 PUFAs is associated with decreased risk of cardiovascular disease (CVD) while consumption of other types of fish are not [3]. Similarly, consumption of fish and n-3 PUFAs has been shown to be positively associated with better heart rate variability indices [4], protective against coronary mortality [5], coronary heart disease (CHD) [6], ischemic heart disease risk [3], CHD related mortality [3], ventricular arrhythmias [7], and all cause mortality post myocardial infarction (MI) [8].

AF has many mechanistic causes and fish-derived n-3 PUFAs may act on some of these mechanisms to prevent AF. Hypothesized biological mechanisms include the putative action of n-3 PUFAs as anti-inflammatory [9] and anti-arrhythmic agents [7].

The literature regarding the association between fish-derived n-3 PUFAs and AF in animal models has been mixed. Some studies have shown that n-3 fatty acid supplementation via food intake protects against stretch-induced vulnerability to atrial fibrillation [10] and that IV supplementation can reduce acute atrial electrophysiological remodeling [11]. However, another animal study demonstrated that n-3 fatty acid food supplementation resulted in proarrhythmia [12]. Consequently, it is unclear whether n-3 fatty acid supplementation affects AF pathogenesis.

Studies in humans have been equally inconsistent. A randomized trial found that n-3 supplementation was associated with decreased incidence of AF in those post CABG [13]. Additionally, the Cardiovascular Health Study, a cohort aged 65 years and older at baseline, also found a lower risk of AF in those with higher n-3 fatty acid intake [14]. However, an analysis of the Rotterdam study [15] and the Health Professionals Follow-up Study [16] found no significant association between n-3 fatty acid consumption and incident AF. Finally, two review studies also concluded against an association [17, 18]. In their review, Den Ruijter et al [17] suggest that the contradictory associations in human studies may be due the pro and anti-arrhythmic properties of n-3 fatty acids, but no empirical data exist to confirm this.

One possible explanation for the inconsistent results in observational studies could be measurement error. A key weakness in both observational studies was the use of dietary data to assess fish-derived n-3 fatty acid intake [14, 15] (it should be noted that the Cardiovascular Health Study had previously demonstrated that dietary questionnaires were correlated with plasma n-3 levels [3], but they used dietary data in their n-3/AF analysis). Thus, it is possible that a plasma measurement of n-3 fatty acids that is less subject to measurement error could better elucidate the relationship between n-3 fatty acids and AF.

The ARIC study would allow for the concurrent study of the association of dietary n-3 fatty acid intake and plasma levels of n-3 fatty acids with the risk of incident AF. Although these two measurements have previously been shown to be correlated [19], separate analysis may give more insight. We propose two analyses: (1) estimate the association between n-3 fatty acids in plasma and the incidence of AF in the Minnesota

component of the ARIC study and (2) investigate the association of n-3 consumption (via fish and other n-3 rich foods) and incidence of AF in the entire ARIC sample.

In addition to considering total n-3 fatty acid levels the ARIC dataset would also allow for the study of individual n-3 fatty acids (alpha-linolenic acid (ALA), and the fish-derived eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) within the plasma data. Previous research in ARIC has shown that individual components of fish-derived n-3 fatty acids can have differing effects on health outcomes [20] and preliminary results from a Finnish cohort aged 42-60 years at baseline demonstrated that DHA is significantly associated with incident AF but that EPA is not [21]. Thus, considering different components of n-3 fatty acids as exposures may yield relevant results.

Because of the mixed literature and the unique data available in ARIC, we propose to determine the association of plasma and dietary n-3 PUFA with the risk of incident AF in ARIC.

## References:

1. Fuster, V., et al., *ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation)*. J Am Coll Cardiol, 2006. **48**(4): p. 854-906.
2. Lloyd-Jones, D., et al., *Heart Disease and Stroke Statistics--2009 Update. A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee*. Circulation, 2008.
3. Mozaffarian, D., et al., *Cardiac benefits of fish consumption may depend on the type of fish meal consumed: the Cardiovascular Health Study*. Circulation, 2003. **107**(10): p. 1372-7.
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7. Leaf, A., et al., *Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils*. Circulation, 2003. **107**(21): p. 2646-52.
8. Breslow, J.L., *n-3 fatty acids and cardiovascular disease*. Am J Clin Nutr, 2006. **83**(6 Suppl): p. 1477S-1482S.
9. Boos, C.J., R.A. Anderson, and G.Y. Lip, *Is atrial fibrillation an inflammatory disorder?* Eur Heart J, 2006. **27**(2): p. 136-49.
10. Ninio, D.M., et al., *Dietary fish oil protects against stretch-induced vulnerability to atrial fibrillation in a rabbit model*. J Cardiovasc Electrophysiol, 2005. **16**(11): p. 1189-94.
11. da Cunha, D.N., et al., *n-3 (omega-3) polyunsaturated fatty acids prevent acute atrial electrophysiological remodeling*. Br J Pharmacol, 2007. **150**(3): p. 281-5.
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13. Calo, L., et al., *N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial*. J Am Coll Cardiol, 2005. **45**(10): p. 1723-8.
14. Mozaffarian, D., et al., *Fish intake and risk of incident atrial fibrillation*. Circulation, 2004. **110**(4): p. 368-73.
15. Brouwer, I.A., et al., *Intake of very long-chain n-3 fatty acids from fish and incidence of atrial fibrillation. The Rotterdam Study*. Am Heart J, 2006. **151**(4): p. 857-62.
16. Lajous, M., et al., *N-3 Polyunsaturated Fatty Acids, Fish Intake, and Risk of New-Onset Atrial Fibrillation: Preliminary Results* Circulation, 2009. **119**(10): p. e307.

17. Den Ruijter, H.M., et al., *Pro- and antiarrhythmic properties of a diet rich in fish oil*. Cardiovasc Res, 2007. **73**(2): p. 316-25.
18. Hooper, L., et al., *Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review*. BMJ, 2006. **332**(7544): p. 752-60.
19. Ma, J., et al., *Plasma fatty acid composition as an indicator of habitual dietary fat intake in middle-aged adults. The Atherosclerosis Risk in Communities (ARIC) Study Investigators*. Am J Clin Nutr, 1995. **62**(3): p. 564-71.
20. Shahar, E., et al., *Dietary n-3 polyunsaturated acids and smoking-related chronic obstructive pulmonary disease*. Am J Epidemiol, 2008. **168**(7): p. 796-801.
21. Virtanen, J.K., et al., *Serum Long-Chain Omega-3 Fatty Acids and Risk of Atrial Fibrillation in Men: The Kuopio Ischemic Heart Disease Risk Factor Study*. Circulation, 2009. **119**(10): p. e314.

## 5. Main Hypothesis/Study Questions:

We hypothesize that the incidence of AF will be lower among those with higher levels of plasma n-3 PUFAs at baseline compared to those at the lowest level. We also hypothesize that the incidence of AF will be lower among those with higher levels of fish intake at baseline compared to those with the lowest intake.

As a secondary aim, we will examine the association between other plasma fatty acids and the risk of AF.

## 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).

### *Exposure assessment*

The plasma n-3 analyses will include individuals from the Minnesota field center of the ARIC cohort (n = 3935) in whom plasma fatty acids were measured at baseline. Plasma n-3 levels in these subjects and the correlation with dietary intake have been documented by Ma et al [19]. The dietary analysis will include subjects from all four field centers (n=15,792).

Independent variables in both analyses include the following as measured at baseline: main exposure (plasma fish-derived n-3 fatty acids (DHA, EPA) or dietary n-3 intake), age, sex, BMI, education, smoking status, alcohol intake, total energy intake, LDL, HDL, use of cholesterol lowering medications, SBP, use of hypertension medications, prevalent diabetes, prevalent CHD, and left ventricular mass. Sensitivity analyses will be performed excluding users of fish supplements.

### *AF ascertainment*

The study outcome for both analyses is incident AF. Incident cases of atrial fibrillation were identified through hospital discharge codes (ICD-9 codes 427.31 and 427.32), ECGs performed during three follow-up visits, and death certificates. Individuals who developed atrial flutter or AF during follow-up will be considered as having an event, and follow-up will be censored at the first occurrence of either AF or

atrial flutter. Individuals without ECG or who had diagnosed AF or atrial flutter at baseline will be excluded from analyses.

#### *Statistical analysis*

We will use Cox proportional hazards regression to determine the hazard ratios of AF by quartiles of n-3 fatty acid levels and categories of fish intake, adjusting for potential confounders. We will also use restricted cubic splines to explore dose-response relationships.

Because presence of coronary heart disease at baseline could be a mediator in the association between n-3 fatty acids/fish intake and the risk of AF, we will conduct additional analysis stratifying by history of cardiovascular disease at baseline.

#### *Limitations*

Limitations for the plasma fatty acids analysis include the small amount of variability in plasma n-3 fatty acid measurements. For the fish intake analysis, data are not available regarding fish preparation methods. Research suggests that fish preparation method is an important determinant of cardiovascular benefit [3]. Finally, both analyses may be limited by a potential lack of power resulting from a small number of AF cases.

#### References:

3. Mozaffarian, D., et al., *Cardiac benefits of fish consumption may depend on the type of fish meal consumed: the Cardiovascular Health Study*. *Circulation*, 2003. **107**(10): p. 1372-7.
19. Ma, J., et al., *Short- and long-term repeatability of fatty acid composition of human plasma phospholipids and cholesterol esters. The Atherosclerosis Risk in Communities (ARIC) Study Investigators*. *Am J Clin Nutr*, 1995. **62**(3): p. 572-8.

**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  
\_\_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 ICTDER02 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.cscce.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)?**

**MS # 1351:** Incidence of atrial fibrillation in a bi-racial cohort: the ARIC study

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

**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\* \_2008.09\_)**

\_\_\_\_ **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.cscce.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.**