ARIC Manuscript Proposal #2805

PC Reviewed: 08/09/16	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Galectin-3 and Atrial Fibrillation Incidence

b. Abbreviated Title (Length 26 characters): Galectin-3 and Atrial Fib

2. Writing Group:

Writing group members: Aaron Folsom, David Aguilar, Christie Ballantyne, Ron Hoogeveen, Lin Y. Chen, Sayed Soliman, Alvaro Alonso

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

First author: Aaron Folsom, although likely this manuscript will be given to an interested student

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3. Timeline: Begin late summer 2016

4. Rationale:

Galectin-3 is a beta-galactoside binding lecitin involved in important regulatory roles in adhesion, inflammation, immunity, and fibrosis. Recent epidemiologic studies have shown galectin-3 is positively associated with incident heart failure and CHD.

Myocardial inflammation and fibrosis are relevant to the etiology of atrial fibrillation. Inhibition of galectin-3 has been shown to interfere with myocardial fibrogenesis, and some have suggested it might be a therapeutic target for atrial fibrillation [pmid: 2660816]. Galectin-3 has been associated with atrial remodeling in atrial fibrillation patients [pmid: 24651058] and outcomes after catheter ablation of atrial fibrillation [pmid 25875595]. To our knowledge, only two prospective studies have tested whether galectin 3 concentrations are associated with incident atrial fibrillation, and both reported positive associations [pmid: 27084804 and 24766984].

Galectin-3 measurements at ARIC visit 4 offer an opportunity to test the following hypothesis:

5. Main Hypothesis/Study Questions:

Plasma galectin-3 concentration is associated positively with incidence of atrial fibrillation.

Secondary: a *LGALS3* (galectin-3 structural gene) locus associated with plasma galectin-3 levels is also associated with atrial fibrillation incidence.

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).

Design: prospective with visit 4 as baseline, with galectin-3 as the exposure (*LGALS3* SNP as secondary)

Outcome: time to incident AF determined from hospital records, exam 5 ECGs, and death certificates.
Exclusions: prevalent AF, HF, CHD; missing galectin-3

Primary Covariates: Main atrial fibrillation risk factors as published by ARIC (age, race, sex, SBP and medications, BMI, height diabetes, smoking, eGFR).

Analysis: Examine association of galectin-3 with covariates. Linear splines to examine association with AF incidence. Main analysis—Cox proportional hazards models. A first model will test race interactions (stratify by race if indicated) and adjust for the main artrial fibrillation risk factors. A second model will adjust further for NT-proBNP, CRP, and troponin T. In a third model we will adjust for left atrial abnormality by V4 ECG (P-terminal force PTF in V1 less than -4000 microvolt). In a secondary analysis, we will consider post V4 HF and CHD as covariates.

The SNP analysis will be conducted assuming an additive genetic model, with and without plasma galectin-3 in the model.

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 ICTDER 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? __x__ 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"? _x___ 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)?
Galectin-3 and Cardiovascular Outcomes (submitted by David Aguilar)

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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes ____ No.