ARIC Manuscript Proposal #2436

PC Reviewed: 9/9/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Galectin 3 and risk heart failure and death in a subsample of the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):

2. Writing Group:

Writing group members: John W (Bill) McEvoy; Yuan Chen; Marc Halushka; Eric Christenson; Christie Ballantyne; Robert Christenson; Elizabeth Selvin; others welcome

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

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3. Timeline: We have recently completed Galectin3 assays in stored specimens from the CARMRI substudy. The data have been transferred to JHU and cleaned. We expect the manuscript to be submitted to ARIC review <1 year from the data of approval.

4. Rationale:

Galectin-3 is in the family of β-galactoside-binding lectins and is expressed on a variety of cell types including monocytes. Galectin-3 is thought to amplify inflammatory processes (1, 2) and may contribute to the development of heart failure (3), atherosclerosis (4), and cancer (5). Nonetheless, the exact pathophysiological role of galectin-3 in these conditions is unclear although it is thought that galectin-3 may have clinical utility as a biomarker of myocardial fibrosis. There is a growing body of literature demonstrating that galectin-3 has prognostic value in patients with existing heart failure (3, 6-9). Indeed, galectin-3 is cited in the American Heart Association clinical guidelines for heart failure as important for "additive risk stratification" in both the ambulatory and acute settings (10). However, more recent data have casted some doubt on the value of Galectin-3 in heart failure prognostication (6). In addition, there have only been a few studies examining the prognostic value of serum galectin-3 in a general population without clinical cardiovascular disease. Galectin-3 was recently shown to be an independent predictor of all-cause mortality in a general population (11) and a nested case-control study in the Physician's Health Study demonstrated that higher levels of plasma galectin-3 were significantly and independently associated with heart failure and that this association was observed among cases of heart failure with and without antecedent coronary heart disease (12). Serum galectin-3 was associated with total mortality and cardiovascular death but not coronary heart disease events in the Rancho Bernardo Study, a population of older adults (mean age, 70) who are predominately white (13). A previous report from 3,353 participants in the Framingham Heart Offspring Cohort also found that galectin 3 was associated with left ventricular mass and risk of heart failure and total mortality; all associations remained significant after adjustment (14). Thus, while Galectin-3 appears to be a promising novel biomarker of cardiac risk,more data from racially diverse populations are needed as this biomarker has, to date, been predominately studied in Caucasian populations.

5. Main Hypothesis/Study Questions:

We propose to examine the prospective association of galectin-3 with heart failure and total mortality in the CARMRI sub-study of the Atherosclerosis Risk in Communities (ARIC) Study. We have measured galectin-3 in all participants who attended the CARMRI visit in 2004-2005 and provided a blood sample. We will identify correlates of galectin-3 at baseline, including possible racial differences. We will evaluate possible effect modification of the association of galectin-3 with incident heart failure, atrial fibrillation, coronary heart disease (CHD) and mortality by age, race, gender, and obesity status at baseline.

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 population: n=2,004 in the subsample of ARIC participants for whom a blood sample was obtained at the CARMRI visit (2004-06) and for which a valid measurement of galectin 3 could be obtained.

Inclusion/Exclusion: persons with a history of heart failure at baseline at baseline (2004-2005) or missing variables of interest will be excluded. Secondary analyses of incident coronary heart disease will exclude persons with a history of CHD at baseline (defined as self-reported CHD at visit 1 or an adjudicated (non-fatal) clinical event or silent MI prior to the date of the CARMRI visit, or silent MI detected at the CARMRI visit).

Study design: Prospective cohort analysis of galectin3 measured in 2004-05 and subsequent heart failure and all-cause mortality using the most recent follow-up datafiles available. We will formally test for interaction by race and conduct race-stratified analyses. We will conduct secondary analyses of incident atrial fibrillation and CHD (among persons free of CHD at baseline). We will also perform cross-sectional analysis of correlates of elevated galectin-3 at baseline. We will use Poisson regression models (or predictive margins from logistic regression) to examine the prevalence ratios of elevated galectin-3 for relevant risk factors listed below to identified "determinants" of elevated galectin-3 at baseline.

Exposure: Galectin-3 measured by ELISA (BG Medicine, Inc.) in stored serum samples.

Outcomes: incident heart failure and all-cause mortality. Heart failure will be defined by hospitalizations with an ICD-9 code of 428 or death with an underlying cause of ICD-9 428 or ICD-10 I50. Secondary analysis: incident atrial fibrillation and coronary heart disease (adjudicated event, procedures, or death).

Covariates: age, sex, race-center, body mass index, total cholesterol, systolic and diastolic blood pressures, blood pressure-lowering medication use, smoking status, diabetes status (self-reported history, medication use, glucose, HbA1c), lipid parameters and C-reactive protein. These variables will also be considered as potential correlates of galectin3 in cross-sectional analyses.

Potential effect modifiers: age, sex, race (black vs white), and obesity status at baseline

Statistical analysis:
All analyses will be weighted by the inverse of the sample fractions in the eight sampling strata (four field centers by two IMT groups) using standard methods.

1) We will examine the characteristics of the study population by quartiles of galectin3 at baseline ("Table 1")
2) Poisson regression models or predictive margins from logistic regression to generate prevalence ratios for the associations of cardiovascular risk factors with high levels of galectin3 at baseline (e.g., Q4 vs Q1-Q3) ("Table 2").

3) Cox regression models and standard survival analysis methods (Kaplan-Meier) will be used to examine the association of galectin3 with incident heart failure and death. Secondary analysis will examine incident atrial fibrillation and coronary heart disease. Initial analyses will examine the associations according to quartiles of galectin-3 at baseline and also using restricted cubic splines to characterize the shape of the associations. The proportional hazards assumption will be examined using log-log plots and by testing risk factor-by-time interactions; if the assumption is violated the interactions term(s) will be kept in the model and the time-dependent nature of the risk will be interpreted accordingly. For associations that appear roughly linear, we may model galectin-3 continuously (e.g, log-transformed). For the analyses of incident coronary heart disease, stroke and mortality, we will examine the potential mediation by the development of heart failure. To address this we will conduct analyses censoring cases of heart failure occurring prior to the other events. Tests for interaction by age, sex, race, and obesity status will be conducted.

Limitations:

- Relatively small sample size and limited follow-up (currently a median 5.8 years for heart failure), especially for subgroup analyses and corresponding low power to detect effect modification
- Single measurement of galectin-3 at baseline
- Lack of adjudication of heart failure events
- Older age of the study population (mean age ~70 years) may limit generalizability of findings
- Cannot fully eliminate the possibility of residual confounding in this observational setting

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?
____ 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)?

2004.11-CARMRI 1211 Determinants of carotid plaque presence and pathology as measured by magnetic resonance imaging: The ARIC Study Wagenknecht, LE

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*2006.02)

___ 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.

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