ORIGINAL RESEARCH

Galectin-3 and Risk of Heart Failure and Death in Blacks and Whites

John W. McEvoy, MB, BCh, BAO, MHS; Yuan Chen, MS; Marc K. Halushka, MD, PhD; Eric Christenson, MD; Christie M. Ballantyne, MD; Roger S. Blumenthal, MD; Robert H. Christenson, PhD; Elizabeth Selvin, PhD, MPH

***Background*—**The association between galectin-3 and heart failure (HF) or death is well established for white, but not for black, adults.

***Methods and Results*—**Galectin-3 was measured in 1809 participants (1375 white, 434 black), enrolled in a substudy of the Atherosclerosis Risk in Communities (ARIC) observational cohort during 2004–2005. We used Cox proportional hazard models to estimate the adjusted association between galectin-3 and outcomes. Analyses were conducted overall and by race category. Median (interquartile range) galectin-3 levels were 13.4 (11.2–16.4) and 14.8 (12–17.6) ng/mL, in white and black participants, respectively. In the sample overall, galectin-3 was not independently associated with HF or death over a maximum of 7.9 years. However, in race-stratified analyses, galectin-3 was independently associated with a composite of HF or death among whites (eg, hazard ratio 2.2, 95% CI 1.2–3.9, comparing Q4 versus Q1); but not among blacks (hazard ratio of 0.8 [0.4–1.8] for Q4 versus Q1, race interaction P=0.03). Associations between galectin-3 and both outcomes analyzed individually also demonstrated similar racial differences. Furthermore, results were qualitatively similar with galectin-3 modeled as a continuous exposure. In addition, galectin-3 improved discrimination for the composite of HF or death among whites (increase in Harrell's C statistic from 0.729 to 0.735 [difference of +0.006], P=0.049), but not among blacks (0.696 to 0.695 [difference of −0.001], P=0.814).

***Conclusions*—**In contrast to whites, galectin-3 may have limited prognostic utility for predicting HF and death in blacks. While our results require replication, they could reflect racial differences in the processes by which galectin-3 mediates disease. **(*J Am Heart Assoc*. 2016;5:e003079 doi: 10.1161/JAHA.115.003079)**

Key Words: biomarker • death • galectin-3 • heart failure • race and ethnicity

Galectin-3, a member of the β-galactoside-binding lectins family, is thought to amplify inflammatory and fibrotic processes,[1] and may contribute directly to the development of atherosclerosis,[2] heart failure,[3] and cancer.[4] Prior research has demonstrated the prognostic value of galectin-3 in patients with existing heart failure,[3,5–7] including in heart failure with preserved ejection fraction.[8] On this basis, galectin-3 received a class IIb endorsement in 2013 American College of Cardiology/American Heart Association heart failure guidelines for use as a myocardial fibrosis biomarker to guide "risk stratification" in both ambulatory and acute settings (of note, galectin-3 was not reviewed in recent European heart failure guidelines).[9,10] However, emerging data have cast some doubt on the prognostic value of galectin-3 in heart failure,[11,12] particularly relative to other fibrosis biomarkers, such as ST2.[13]

Despite emerging uncertainty regarding the independent value of galectin-3 in the setting of established heart failure, there is compelling evidence that galectin-3 may also be an effective biomarker of future risk for new-onset heart failure or mortality in overtly asymptomatic persons. Specifically, galectin-3 has previously been shown to be an independent predictor of all-cause mortality in a general population study of whites from the Netherlands[14]; all-cause mortality and cardiovascular disease death in the U.S. Rancho Bernardo Study[15]; and heart failure in a nested case–control study from the U.S. Physician's Health Study.[16] Consistent with these results, a report from the Framingham Heart Offspring study also found

From the Department of Epidemiology and the Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (J.W.M., Y.C., E.S.); Ciccarone Center for the Prevention of Heart Disease (J.W.M., R.S.B.) and Departments of Pathology (M.K.H.) and Medicine (E.C.), Johns Hopkins University School of Medicine, Baltimore, MD; Section of Cardiovascular Research, Department of Medicine, Baylor College of Medicine and Houston Methodist DeBakey Heart and Vascular Center, Houston, TX (C.M.B.); Department of Pathology, University of Maryland School of Medicine, Baltimore, MD (R.H.C.).

Accompanying Tables S1, S2 and Figure S1 are available at http://jaha.ahajournals.org/content/5/5/e003079/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Elizabeth Selvin, PhD, MPH, Welch Center for Prevention, Epidemiology and Clinical Research and the Johns Hopkins Bloomberg School of Public Health, 2024 E, Monument Street, Suite 2-600, Baltimore, MD 21287. E-mail: eselvin@jhu.edu

Received December 14, 2015; accepted April 19, 2016.

that galectin-3 was independently associated with left ventricular mass, risk of incident heart failure, and total mortality.[17]

However, while the above reports suggest a potential role for galectin-3 as a biomarker for heart failure risk in primary prevention settings, these data were derived from almost exclusively white study populations, and further research from racially diverse populations is needed. Thus, we sought to evaluate the association between baseline galectin-3 and heart failure and death in a substudy of 1375 white and 434 black participants from the Atherosclerosis Risk in Communities (ARIC) Study.

Methods

Study Population

ARIC is an ongoing prospective cohort study of 15 792 subjects, enrolled between 1987 and 1989 from four U.S. communities (Forsyth Country, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland).[18] Galectin-3 was measured in 2005 ARIC participants who attended the carotid magnetic resonance imaging (CARMRI) substudy in 2004–2005. The ARIC CARMRI substudy was designed to investigate correlates of carotid atherosclerosis imaged using high-resolution contrast-enhanced MRI.[19] The study was approved by the institutional review boards of the participating institutions, and all participants gave informed consent.

Stratified sampling, designed to enrich the sample with carotid atherosclerosis but still allow inferences to be drawn from the entire ARIC population, was used to select CARMRI participants.[19] All of the 2005 participants included had blood drawn for measurement of galectin-3. For the purposes of our main analysis of incident heart failure and death, we excluded 122 persons with baseline heart failure and 74 persons with missing data, resulting in an analytic sample of 1809 (Table S1).

Table 1. Baseline Characteristics of the Analytic Sample; Overall and by Galectin-3 Quartile (N=1809)

	Overall	Q1	Q2	Q3	Q4	*P* Value
Galectin-3, range in ng/mL	4.2 to 184.1	4.2 to 11.38	11.4 to 13.8	13.8 to 16.7	16.7 to 184.1	
Age, mean (SD), y	71.0 (5.6)	69.7 (5.2)	70.4 (5.4)	71.2 (5.3)	72.8 (5.9)	<0.001
Female, %	51.0	36.6	54.3	52.5	60.4	<0.001
Black, %	24.0	18.3	20.1	28.2	29.4	<0.001
Body mass index (BMI), %						0.021
Normal weight (<25 kg/m^2)	23.9	26.0	24.1	23.1	22.3	
Overweight (25–30 kg/m^2)	41.8	46.6	41.5	40.1	38.9	
Obese (>30 kg/m^2)	34.3	27.4	34.4	36.8	38.7	
Mean (SD) BMI	28.7 (5.1)	28.0 (4.7)	28.7 (5.0)	28.8 (5.0)	29.3 (5.6)	<0.001
Smoking status, %						0.061
Never smoked	45.6	41.3	45.0	44.3	51.5	
Current smoker	8.8	8.4	10.2	9.3	7.5	
Former smoker	45.6	50.3	44.8	46.3	40.9	
Total cholesterol, mean (SD) in mg/dL	193.1 (41.0)	195.2 (41.9)	192.0 (39.4)	190.9 (41.3)	194.1 (41.4)	0.314
High total cholesterol (≥200 mg/dL), %	41.0	41.7	40.2	39.2	42.9	0.685
HDL, mean (SD) in mg/dL	49.2 (14.5)	50.5 (15.5)	49.8 (14.4)	48.7 (14.5)	48.0 (13.6)	0.061
Low HDL cholesterol, %*	40.9	33.8	39.1	44.3	46.2	<0.001
Systolic blood pressure, mean (SD) in mm Hg	127.2 (18.9)	127.2 (17.9)	126.2 (18.3)	126.7 (18.9)	128.8 (20.3)	0.191
Hypertension, %†	74.8	66.2	70.9	78.9	83.4	<0.001
Hemoglobin A1c %, mean (SD)	5.8 (0.8)	5.8 (0.8)	5.8 (0.7)	5.9 (0.9)	5.9 (0.8)	0.018
Diabetes, %‡	32.9	30.5	29.6	33.9	37.6	0.041
Low eGFR (<60 mL/min per 1.73 m^2), %	19.7	6.8	10.2	21.3	40.7	<0.001
Cardiovascular disease at baseline, %	14.7	12.6	13.9	16.6	15.7	0.314

eGFR indicates estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; Q, quartile.
*Low HDL cholesterol is defined as <40 mg/dL for men and <50 mg/dL for women.
†Hypertension is defined as diastolic blood pressure ≥90 mm Hg, systolic blood pressure ≥140 mm Hg, or blood pressure–lowering medication use.
‡Diabetes is defined as self-report doctor diagnosed or medication use, fasting glucose ≥126 mg/dL, or hemoglobin A1c ≥6.5%.

Table 2. Baseline Characteristics of the Analytic Sample; Overall and by Race (N=1809)

	Overall	Whites (N=1375)	Blacks (N=434)	*P* Value
Galectin-3, range in ng/mL	4.2 to 184.1	4.2 to 184.1	6.2 to 87.5	
Age, y	71.0 (5.6)	71.3 (5.5)	70.1 (5.8)	<0.001
Female, %	51.0	48.0	60.4	<0.001
Black, %	24.0	0.0	100.0	<0.001
Body mass index (BMI), %				<0.001
Normal weight (<25 kg/m^2)	23.9	26.3	16.4	
Overweight (25–30 kg/m^2)	41.8	42.7	38.9	
Obese (>30 kg/m^2)	34.3	31.1	44.7	
Mean (SD) BMI	28.7 (5.1)	28.2 (4.8)	30.1 (5.6)	<0.001
Smoking status, %				<0.001
Never smoked	45.6	43.6	51.6	
Current smoker	8.8	8.1	11.1	
Former smoker	45.6	48.2	37.3	
Total cholesterol, mean (SD) in mg/dL	193.1 (41.0)	190.7 (40.7)	200.5 (41.0)	<0.001
High total cholesterol (≥200 mg/dL), %	41.0	38.8	48.2	<0.001
HDL, mean (SD) in mg/dL	49.2 (14.5)	48.6 (14.6)	51.4 (14.1)	<0.001
Low HDL cholesterol, %*	40.9	42.5	35.7	0.013
Systolic blood pressure, mean (SD) in mm Hg	127.2 (18.9)	126.5 (18.4)	129.3 (20.4)	<0.001
Hypertension, %†	74.8	72.1	83.6	<0.001
Hemoglobin A1c %, mean (SD)	5.8 (0.8)	5.7 (0.6)	6.2 (1.1)	<0.001
Diabetes, %‡	32.9	29.2	44.7	<0.001
Low eGFR (<60 mL/min per 1.73 m^2), %	19.7	20.0	18.9	0.614
Cardiovascular disease at baseline, %	14.7	15.6	11.8	0.046

eGFR indicates estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol.
*Low HDL cholesterol is defined as <40 mg/dL for men and <50 mg/dL for women.
†Hypertension is defined as diastolic blood pressure ≥90 mm Hg, systolic blood pressure ≥140 mm Hg, or blood pressure–lowering medication use.
‡Diabetes is defined as self-report doctor diagnosed or medication use, fasting glucose ≥126 mg/dL, or hemoglobin A1c ≥6.5%.

Measurement of Galectin-3 and Other Exposure Variables

Galectin-3 was measured in 2013 in stored serum samples using the BGM Galectin-3 assay, an ELISA on a microtiter plate platform (BG Medicine, Waltham, MA). This Galectin-3 assay has been characterized previously.[1] For this study the testing was completed in 59 analytic runs; the low control demonstrated a mean of 19.0 ng/mL, SD 1.0 ng/mL, interassay CV 5.3%, and the high control showed a mean value of 64.1 ng/mL, SD 2.9 ng/mL, and interassay CV of 4.5%. The 2 subjects with Galectin-3 values >94.8 ng/mL underwent sample dilution as per manufacturer instructions. Otherwise, fasting blood samples were assayed for total and high-density lipoprotein (HDL) cholesterol, as well as fasting glucose using conventional techniques.[19] Glomerular filtration rate was estimated using serum creatinine and the CKD-EPI 2009 equation (eGFR).

The CARMRI core examination procedures were identical to those previously established for prior ARIC visits.[18,19] Standardized ARIC procedures have been previously described for the measurement of blood pressure and determination of body mass index (in kg/m^2). Diabetes was defined as self-report of a doctor diagnosis, medication use, fasting glucose ≥126 mg/dL, or hemoglobin A1c ≥6.5%. To ascertain medication use, participants were asked to bring containers of current medications to the CARMRI visit. Participants self-reported race and smoking status.

Outcome Ascertainment: Heart Failure and Death

The methods for ascertainment of deaths and adjudication of cardiovascular events in ARIC have been previously published.[20] Briefly, any hospitalization was reported annually by participants or their proxy and also identified through

Table 3. Adjusted* Prevalence Ratios (PRs) for the Highest Quartile of Galectin-3 (Unweighted N=1809); Overall and Stratified by Race

	Overall	White (N=1375)	Black (N=434)
	PR (95% CI)	PR (95% CI)	PR (95% CI)
Age, per 10 y	1.63 (1.34–1.97) †	1.80 (1.41–2.30) †	1.26 (0.94–1.69)
Female (vs male)	1.32 (1.07–1.62) †	1.32 (1.03–1.68) †	1.37 (0.95–2.00)
Black (vs white)	1.37 (1.11–1.70) †	—	—
Body mass index, kg/m^2			
25–30 (vs <25)	1.03 (0.78–1.35)	1.05 (0.77–1.43)	0.96 (0.56–1.64)
≥30 (vs <25)	1.22 (0.92–1.60)	1.16 (0.84–1.61)	1.29 (0.77–2.17)
Cigarette smoking			
Current smoker (vs never)	0.90 (0.61–1.33)	0.85 (0.51–1.41)	0.91 (0.49–1.69)
Former smoker (vs never)	0.94 (0.76–1.16)	0.97 (0.76–1.25)	0.84 (0.58–1.22)
High total cholesterol (≥200 mg/dL), yes/no	1.19 (0.96–1.48)	1.31 (1.01–1.69)	0.91 (0.64–1.30)
Low HDL cholesterol‡, yes/no	1.31 (1.07–1.61)†	1.28 (1.00–1.63)	1.35 (0.94–1.94)
Hypertension§, yes/no	1.07 (0.82–1.39)	1.11 (0.81–1.51)	0.94 (0.60–1.48)
Diabetes‖, yes/no	1.05 (0.86–1.29)	1.22 (0.95–1.56)	0.74 (0.53–1.05)
Low eGFR¶, yes/no	2.34 (1.92–2.86)†	2.35 (1.85–3.00)†	2.44 (1.75–3.39)†

ARIC indicates Atherosclerosis Risk in Communities; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol.
*Poisson model adjusted for all variables listed above and are weighted, where the number observed to be at risk (N=1809) is reweighted to reflect the entire available ARIC cohort (N=4731) using a stratified sampling design.
†$P<0.05$.
‡Low HDL cholesterol is defined as <40 mg/dL for men and <50 mg/dL for women.
§Hypertension is defined as diastolic blood pressure ≥90 mm Hg, systolic blood pressure ≥140 mm Hg, or antihypertensive medication use.
‖Diabetes is defined as self-report doctor-diagnosed diabetes or medication use, fasting glucose ≥126 mg/dL, or hemoglobin A1c ≥6.5%.
¶Low eGFR is defined as <60 mL/min per 1.73 m^2.

surveillance of hospitals in each ARIC community. Trained personnel abstracted hospital records for potential cardiovascular events. Heart failure cases were identified from hospitalization diagnosis codes (ICD-9 code 428) and deaths by surveillance (hospital discharge records for inpatient deaths and death certificates for deaths outside the hospital).[21] The primary outcome for this analysis was the composite of heart failure or death; we also report findings for each outcome individually. Participants were administratively censored for events in December 31, 2012.

Statistical Analyses

The analytic plan was submitted as a prespecified proposal to the ARIC internal review committee prior to commencing analyses. In keeping with prior studies,[17] characteristics for the study population were tabulated according to quartiles of galectin-3 and were compared using ANOVA for continuous variables or χ^2 testing for proportions. To facilitate generalization to the entire ARIC cohort, all analyses were weighted by the inverse of the sample fractions in the CARMRI sampling strata using standard methods. We used Poisson regression to estimate adjusted prevalence ratios for the highest quartile of galectin-3 based on risk factors measured at baseline. Negative binomial models were also used to estimate prevalence ratios, and the results from these models were nearly identical to those from our Poisson models, with no evidence of overdispersion (α close to zero).

Cumulative survival curves were generated using the Kaplan–Meier method. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and their 95% CIs for heart failure and death, both as a composite outcome and individually. Galectin-3 was modeled as both a categorical (quartiles) and a continuous exposure (log-transformed). *P*-values for linear trends across galectin-3 quartiles were obtained by assigning the median galectin-3 value in each quartile and modeling this ordinal variable continuously. For all models, we verified the proportionality of the hazards with Schoenfeld residuals.

Models were adjusted for age (years), race-center (whites–Washington County; whites–Minneapolis; blacks–Jackson; blacks–Forsyth County, whites–Forsyth County), sex (male or female), smoking status (current, former, or never), diabetes status (yes or no), mean systolic blood pressure (mm Hg), mean diastolic blood pressure (mm Hg), antihypertensive medication use (yes or no), total cholesterol

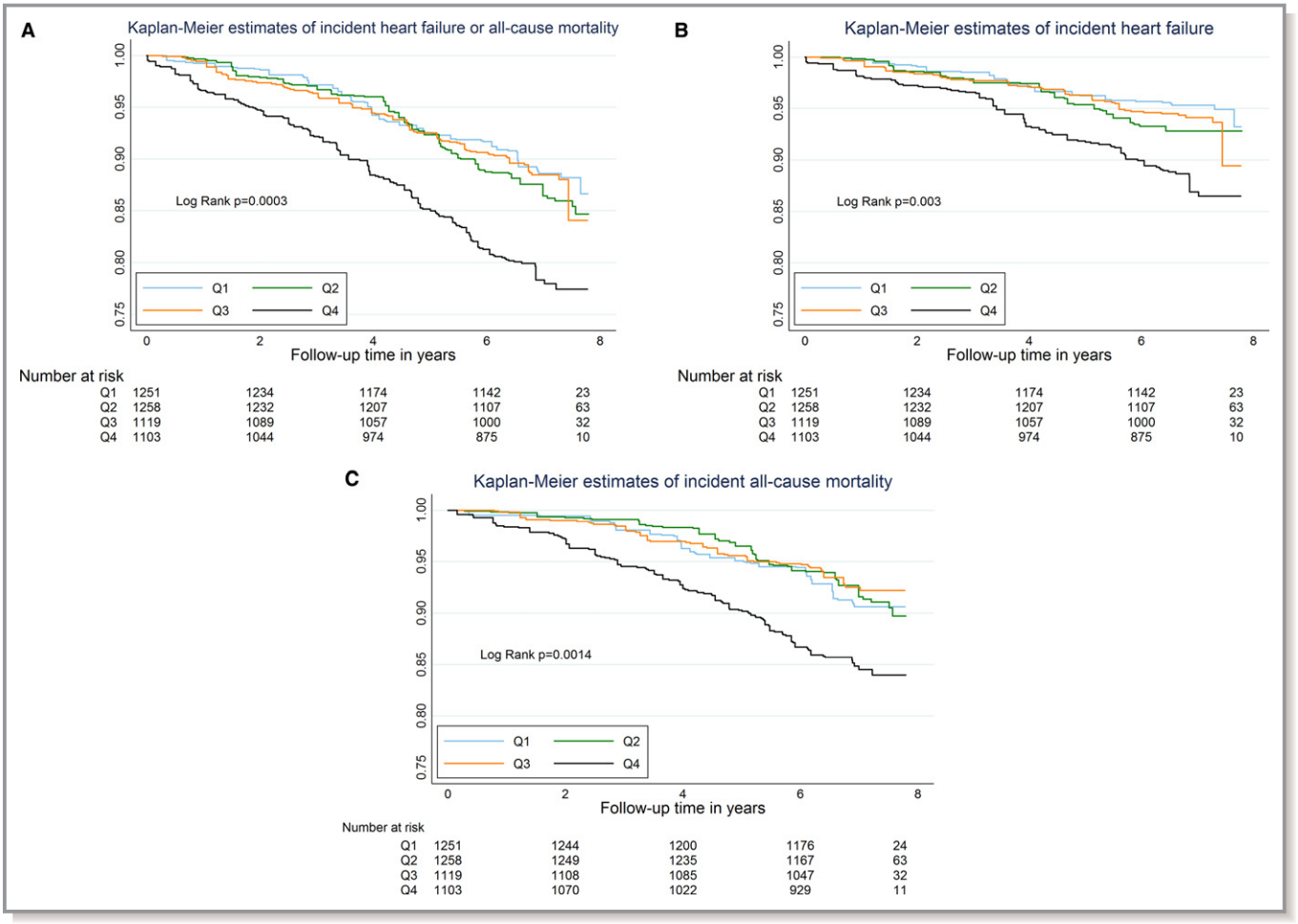

Figure 1. Kaplan–Meier estimates of survival free from the composite outcome of heart failure or death (A), incident heart failure (B), and death (C), according to baseline galectin-3 quartile, in a community-based asymptomatic sample from ARIC (unweighted N=1809). This is a weighted Kaplan–Meier, where the number observed to be at risk (N=1809) is reweighted to reflect the entire available ARIC cohort (N=4731) using a stratified sampling design. Log-rank *P*-values are for differences across all 4 quartiles. ARIC indicates Atherosclerosis Risk in Communities.

(mg/dL), HDL cholesterol (mg/dL), and eGFR (continuous, in mL/min per 1.73 m^2). In the Poisson models reporting prevalence ratios, age was rescaled to per 10-year increment. The above variables were chosen based on directed acyclic graphs designed to illustrate the proposed causal link between galectin-3 and events. Model discrimination was assessed using Harrell's C-statistic,[22] and we evaluated improvement in the C-statistic for the addition of galectin-3 as a log-transformed continuous variable to the fully adjusted model. In sensitivity analyses, we additionally adjusted for history of any cardiovascular disease at baseline. We tested for interactions by age, sex, and race group.

We also modeled galectin-3 using linear splines in fully adjusted Cox models for both heart failure and all-cause mortality. A two-sided $P<0.05$ was considered statistically significant. All analyses were performed using Stata version 13.0 (StataCorp, College Station, TX).

Results

In our community-based sample of 1809 subjects, without baseline heart failure, the mean age was 71 years, 51% were female, and 24% were black. Other demographic variables, overall and stratified by galectin-3, are presented in Table 1. Compared to those in the lowest quartile, persons in the highest quartile of galectin-3 were older, more likely to be female, obese, hypertensive, diabetic, and have lower HDLc-holesterol and eGFR <60 mL/min per 1.73 m^2 (Table 1). In addition, there were more blacks in the higher quartiles of galectin-3. In contrast, the crude prevalence of current smoking was marginally lower in the fourth quartile of galectin-3. Race-stratified demographics are presented in Table 2.

Median (interquartile range) galectin-3 levels were 13.4 (11.2–16.4) and 14.8 (12–17.6) ng/mL, in white and black participants, respectively. The continuous distribution of galectin-3 within each race category is demonstrated in

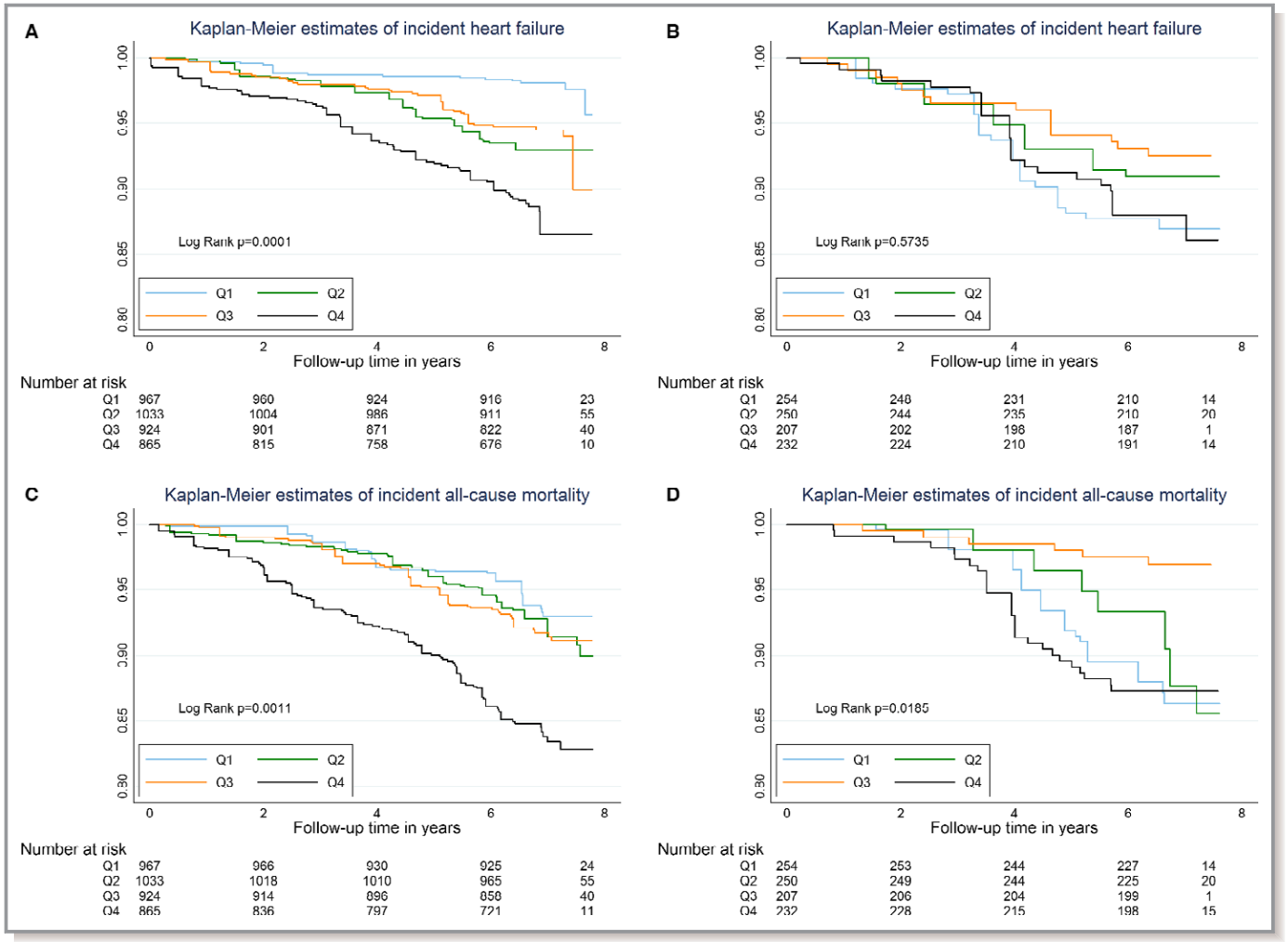

Figure 2. Kaplan–Meier (KM) estimates of survival free from incident heart failure or death, according to galectin-3 quartile, stratified by race (unweighted N=1809). A=KM of incident HF in whites, B=KM of incident HF in blacks, C=KM of death in whites, D=KM of death in blacks. See Figure 1 legend.

Figure S1. In adjusted analyses evaluating cross-sectional associations between baseline demographics and elevated galectin-3 levels, age, female sex, black race, low HDL cholesterol, and, particularly, eGFR <60 mL/min per 1.73 m^2 were all independently associated with prevalent galectin-3 levels in the fourth quartile (Table 3). However, after adjustment, smokers did not have lower galectin-3 levels. Findings for race-stratified prevalence ratios were similar.

Over a median of 6.8 years and a maximum of 7.9 years follow-up, the composite outcome of heart failure or death occurred in 313 participants. There were 167 episodes of incident heart failure and 212 deaths in the sample overall. The incidence rate for heart failure (per 1000 person-years) was 13.4 for whites and 18.1 for blacks overall. Incidence rate for death was 18.3 for whites and 16.4 for blacks. Persons in the highest quartile of galectin-3 had the highest cumulative risk of the composite outcome and both heart failure and death outcomes individually (Figure 1). In contrast, survival curves for those in the first, second, and third quartiles of galectin-3 overlapped and were similar for each outcome. After stratification by race, Kaplan–Meier curves for whites also demonstrates reduced survival in the fourth quartile with overlapping survival in the lower 3 quartiles; however, among blacks the survival appeared to overlap irrespective of galectin-3 status (Figure 2).

In demographic (age-, sex-, and race-adjusted) Cox proportional hazards models, there was a significant association between elevated baseline galectin-3 and the primary composite outcome in the sample overall (eg, HR of 1.72 [1.12–2.62], for Q4 versus Q1; Table 4). However, in fully adjusted models in the sample overall (inclusive of correction for eGFR as a continuous variable), the HRs for increasing quartiles of galectin-3 were no longer statistically significant for the composite outcome, or for heart failure or death individually (eg, HRs of 1.50 [0.93, 2.39], 1.55 [0.77, 3.09], and 1.37 [0.78, 2.41], for Q4 versus Q1, respectively). These

Table 4. Adjusted Hazard Ratios (HRs) for Events; by Baseline Galectin-3 Modeled as a Categorical and Continuous Exposure (Unweighted N=1809)

		Model 1		Model 2	
Galectin-3, ng/mL	Events (n)	HR	*P* Value	HR	*P* Value
Composite outcome (heart failure or death)					
Categorical exposure					
Quartile 1 (4.2–11.4)	55	1 (ref)	—	1 (ref)	—
Quartile 2 (>11.4–13.8)	68	1.24 (0.79–1.94)	0.351	1.13 (0.72–1.77)	0.59
Quartile 3 (>13.8–16.7)	70	1.05 (0.66–1.68)	0.835	0.97 (0.61–1.56)	0.912
Quartile 4 (>16.7–184.1)	120	1.72 (1.12–2.62)	0.013	1.50 (0.93–2.39)	0.094
P-value for trend		0.026		0.147	
Continuous exposure					
log(Galectin 3)	313	1.52 (1.05–2.20)	0.028	1.42 (0.94–2.14)	0.097
Heart failure					
Categorical exposure					
Quartile 1 (4.2–11.4)	27	1 (ref)	—	1 (ref)	—
Quartile 2 (>11.4–13.8)	35	1.52 (0.81–2.86)	0.189	1.38 (0.74–2.58)	0.315
Quartile 3 (>13.8–16.7)	40	1.24 (0.64–2.40)	0.521	1.14 (0.58–2.25)	0.707
Quartile 4 (>16.7–184.1)	65	1.96 (1.07–3.61)	0.03	1.55 (0.77–3.09)	0.218
P-value for trend		0.057		0.322	
Continuous exposure					
log(Galectin 3)	167	1.69 (1.05–2.73)	0.032	1.47 (0.85–2.55)	0.166
Death					
Categorical exposure					
Quartile 1 (4.2–11.4)	37	1 (ref)	—	1 (ref)	—
Quartile 2 (>11.4–13.8)	43	0.91 (0.53–1.57)	0.727	0.84 (0.48–1.47)	0.542
Quartile 3 (>13.8–16.7)	45	0.80 (0.46–1.40)	0.439	0.75 (0.43–1.32)	0.321
Quartile 4 (>16.7–184.1)	87	1.52 (0.92–2.51)	0.103	1.37 (0.78–2.41)	0.266
P-value for trend		0.129		0.301	
Continuous exposure					
log(Galectin 3)	212	1.55 (0.99–2.45)	0.058	1.51 (0.91–2.51)	0.111

ARIC indicates Atherosclerosis Risk in Communities; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol.
Model 1: adjusted for age (yrs), race-center (whites–Washington County; whites–Minneapolis; blacks–Jackson; blacks–Forsyth County, whites–Forsyth County), and sex (male or female).
Model 2: adjusted for age (yrs), race-center (whites–Washington County; whites–Minneapolis; blacks–Jackson; blacks–Forsyth County, whites–Forsyth County), sex (male or female), smoking status (current, former, or never), mean systolic blood pressure (mm Hg), mean diastolic blood pressure (mm Hg), antihypertensive medication use (yes or no), total cholesterol (mg/dL), HDL cholesterol (mg/dL), diabetes status (self-reported history, medication use, glucose, HbA1c), and eGFR (mL/min per 1.73 m^2). Note that Cox models are weighted, where the number observed to be at risk (N=1809) is reweighted to reflect the entire available ARIC cohort (N=4731) using a stratified sampling design.

results were not appreciably altered after further adjustment for history of cardiovascular disease at baseline (Table S2). In addition, when galectin-3 was modeled as a continuous exposure (log-transformed), the fully adjusted HRs for events all remained nonsignificant in the sample overall (Table 4).

While there was no evidence of statistical interaction based on age or sex, we did find interaction by race for the composite (*P*-for-interaction=0.03) and the heart failure outcome (*P*-for-interaction=0.004), but not for all-cause mortality (P-for-interaction=0.17). In fully adjusted analyses stratified by race and using race-specific quartiles, white ARIC participants had significantly elevated risk for the composite outcome of heart failure or death (eg, HR of 2.15 [1.20, 3.88], for Q4 versus Q1, Table 5). Results for this composite outcome with galectin-3 modeled continuously were also significant among whites (Table 5 and Figure 3). In contrast, there was no association present in blacks (eg, HR of 0.83 [0.38, 1.82], for Q4 versus Q1; and HR 0.60 [0.18–2.01] for galectin-3 modeled as a continuous exposure). Given the Kaplan–Meier findings, we conducted sensitivity analyses

Table 5. Fully Adjusted* Hazard Ratios (HRs) for Events; by Baseline Galectin-3 Modeled as a Categorical and Continuous Exposure (Unweighted N=1809); Stratified by Race and Using Race-Specific Quartiles

	White (N=1375)			Black (N=434)		
Galectin-3, ng/mL	n/N	HR	*P* Value	n/N	HR	*P* Value
Composite outcome (heart failure or death)						
Categorical exposure						
Quartile 1	33/344	1 (ref)	—	20/109	1 (ref)	—
Quartile 2	54/344	1.43 (0.82–2.51)	0.21	12/108	0.82 (0.34–2.00)	0.668
Quartile 3	57/344	1.48 (0.84–2.61)	0.174	15/109	0.46 (0.20–1.08)	0.074
Quartile 4	97/343	2.15 (1.20–3.88)	0.01	25/108	0.83 (0.38–1.82)	0.638
P-value for trend		0.014			0.409	
Continuous exposure						
log(Galectin 3)	241/1375	1.70 (1.10–2.63)	0.016	72/434	0.60 (0.18–2.01)	0.408
Heart failure						
Categorical exposure						
Quartile 1	14/344	1 (ref)	—	14/109	1 (ref)	—
Quartile 2	24/344	2.49 (1.08–5.71)	0.032	7/108	0.78 (0.25–2.48)	0.677
Quartile 3	31/344	2.38 (1.00–5.68)	0.05	12/109	0.58 (0.22–1.55)	0.276
Quartile 4	49/343	2.86 (1.13–7.25)	0.027	16/108	0.89 (0.35–2.29)	0.813
P-value for trend		0.095			0.702	
Continuous exposure						
log(Galectin 3)	118/1375	1.74 (0.96–3.15)	0.069	49/434	0.75 (0.18–3.04)	0.685
Death						
Categorical exposure						
Quartile 1	21/344	1 (ref)	—	12/109	1 (ref)	—
Quartile 2	37/344	1.05 (0.53–2.09)	0.889	8/108	0.90 (0.33–2.42)	0.828
Quartile 3	38/344	1.19 (0.61–2.32)	0.609	6/109	0.23 (0.07–0.72)	0.012
Quartile 4	70/343	1.91 (0.94–3.87)	0.073	20/108	1.14 (0.48–2.71)	0.767
P-value for trend		0.054			0.782	
Continuous exposure						
log(Galectin 3)	166/1375	1.79 (1.05–3.03)	0.032	46/434	0.79 (0.19–3.24)	0.740

ARIC indicates Atherosclerosis Risk in Communities; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol.
White galectin-3 Quartiles (ng/mL): 4.2 to 11.2, >11.2 to 13.4, >13.4 to 16.4, >16.4 to 184.1. Black galectin-3 Quartiles (ng/mL): 6.2 to 12, >12 to 14.8, >14.8 to 17.6, >17.6 to 87.5
*Adjusted for age (years), race-center (whites–Washington County; whites–Minneapolis; blacks–Jackson; blacks–Forsyth County, whites–Forsyth County), sex (male or female), smoking status (current, former, or never), mean systolic blood pressure (mm Hg), mean diastolic blood pressure (mm Hg), antihypertensive medication use (yes or no), total cholesterol (mg/dL), HDL cholesterol (mg/dL), diabetes status (self-reported history, medication use, glucose, HbA1c), and eGFR (mL/min per 1.73 m^2). Note that Cox models are weighted, where the number observed to be at risk (N=1809) is reweighted to reflect the entire available ARIC cohort (N=4731) using a stratified sampling design.

comparing the fourth quartile of galectin-3 to the bottom 3 quartiles (Q4 versus Q1–3) and found a persistent association among whites (HR 1.59 [1.05, 2.41]) for the composite outcome, but again no association for blacks (HR 1.09 [0.60, 1.99]).

Racial differences in the association between galectin-3 were also present for each of the individual outcomes. Parsimonious demographic adjusted models demonstrated increased risk for both heart failure and death among whites, but no association between galectin-3 and events among blacks (Table 6). Furthermore, in the fully adjusted model, there was also increased risk for heart failure (2.86 [1.13, 7.25]) and nominally increased risk for all-cause mortality (1.91 [0.94, 3.87]), comparing the fourth quartile of galectin-3 to the first among whites (Table 5). Race-stratified results with galectin-3 modeled as a continuous exposure demonstrated a significant association between galectin-3 and death in whites (1.79 [1.05–3.03]). These HRs among whites contrast with HRs of 0.89 (0.35–2.29) for heart failure and 1.14 (0.48–2.71) for death, in the fourth versus first quartiles among blacks, with

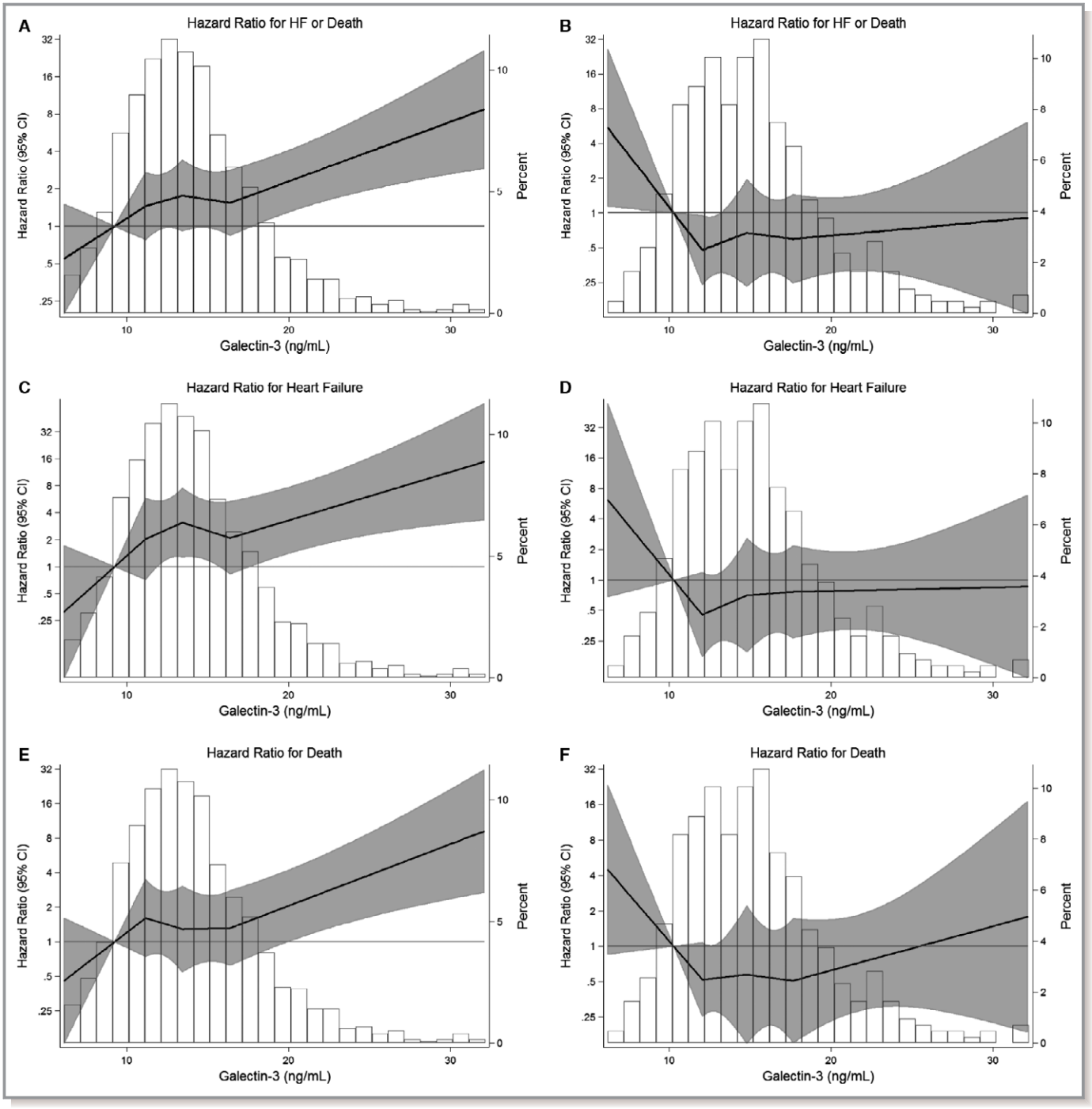

Figure 3. Adjusted hazard ratio (95% CI) for events, according to baseline galectin-3 (ng/mL) modeled as linear splines (knots at quartiles and centered at the 10th percentile), with background histogram of galectin-3 values in the sample; stratified by race (A=HF or death among whites, B=HF or death among blacks, C=HF among whites, D=HF among blacks, E=death among whites, F=death among blacks). Adjusted for age (years), race-center (whites–Washington County; whites–Minneapolis; blacks–Jackson; blacks–Forsyth County, whites–Forsyth County), sex (male or female), smoking status (current, former, or never), mean systolic blood pressure (mm Hg), mean diastolic blood pressure (mm Hg), antihypertensive medication use (yes or no), total cholesterol (mg/dL), HDL cholesterol (mg/dL), diabetes status (self-reported history, medication use, glucose, HbA1c), and eGFR (mL/min per 1.73 m^2). Weighted Cox models, where the number observed to be at risk (N=1809) is reweighted to reflect the entire available ARIC cohort (N=4731) using a stratified sampling design. Linear splines of hazard for events with background distributional histogram of baseline galectin-3 levels, truncated at the 1st and 99th percentile before model fitting. Note that the "Percent" axis label identifies the percentage of the ARIC analytic sample at each point on this background histogram. The shaded area around the regression line represents the 95% CI. ARIC indicates Atherosclerosis Risk in Communities; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure.

Table 6. Demographic Adjusted* Hazard Ratios (HRs) for Events; by Baseline Galectin-3 Modeled as a Categorical and Continuous Exposure (Unweighted N=1809); Stratified by Race and Using Race-Specific Quartiles

	White (N=1375)			Black (N=434)		
Galectin-3, ng/mL	n/N	HR	*P* Value	n/N	HR	*P* Value
Heart failure						
Categorical exposure						
Quartile 1	14/344	1 (ref)	—	14/109	1 (ref)	—
Quartile 2	24/344	3.09 (1.31–7.32)	0.01	7/108	0.71 (0.23–2.19)	0.551
Quartile 3	31/344	2.75 (1.16–6.54)	0.022	12/109	0.53 (0.20–1.42)	0.204
Quartile 4	49/343	4.32 (1.87–9.99)	<0.001	16/108	0.81 (0.34–1.95)	0.638
P-value for trend		0.002			0.581	
Continuous exposure						
log(Galectin 3)	118/1375	1.99 (1.24–3.19)	0.005	49/434	0.76 (0.18–3.22)	0.705
Death						
Categorical exposure						
Quartile 1	21/344	1 (ref)	—	12/109	1 (ref)	—
Quartile 2	37/344	1.20 (0.60–2.38)	0.604	8/108	0.79 (0.28–2.25)	0.662
Quartile 3	38/344	1.30 (0.66–2.57)	0.446	6/109	0.21 (0.07–0.65)	0.007
Quartile 4	70/343	2.18 (1.14–4.15)	0.018	20/108	0.90 (0.37–2.23)	0.826
P-value for trend		0.013			0.548	
Continuous exposure						
log(Galectin 3)	166/1375	1.74 (1.10–2.74)	0.017	46/434	0.70 (0.15–3.29)	0.646

ARIC indicates Atherosclerosis Risk in Communities.
White galectin-3 Quartiles (ng/mL): 4.2 to 11.2, >11.2 to 13.4, >13.4 to 16.4, >16.4 to 184.1. Black galectin-3 Quartiles (ng/mL): 6.2 to 12, >12 to 14.8, >14.8 to 17.6, >17.6 to 87.5
*Adjusted for age (yrs), race-center (whites–Washington County; whites–Minneapolis; blacks–Jackson; blacks–Forsyth County, whites–Forsyth County), and sex (male or female). Note that Cox models are weighted, where the number observed to be at risk (N=1809) is reweighted to reflect the entire available ARIC cohort (N=4731) using a stratified sampling design.

similar null associations when galectin-3 was modeled as a continuous exposure in blacks (Table 5, Figure 3).

Finally, the addition of galectin-3 to the fully adjusted model increased the C-statistic for the composite outcome of heart failure or death in the sample overall (0.713–0.718 [+0.005], *P*=0.037). Consistent with the above findings, this was driven by a significant increase in discrimination among whites (0.729–0.735 [+0.006], *P*=0.049), but no change among blacks (0.696–0.695 [−0.001], *P*=0.814).

Discussion

In this biracial sample of community-based adults, we found that, overall, galectin-3 was not independently associated with incident heart failure or all-cause mortality over a median follow-up of 6.8 years. However, there was significant interaction based on race, and, after stratification, galectin-3 was revealed as a significant risk factor for the composite of heart failure or mortality in white participants, but not in black subjects. Similar racial differences were also present for heart failure and mortality as individual outcomes. Indeed, the HR point estimates for elevated galectin-3 were consistently less than 1 among blacks. Therefore, the null association between galectin-3 and outcomes in the sample overall appears to have been driven by null associations in blacks.

Our results extend the literature in this field, particularly as prior reports of galectin-3 as a risk factor for incident outcomes were all derived from cohorts comprised almost exclusively of white participants.[14,15,17] A major question for the interpretation of our race-stratified results is whether the lack of association between galectin-3 and our outcomes of interest is due to biological heterogeneity for galectin-3 among different racial categories (eg, no causal effect in blacks) or whether the stratified analysis by race in this sample was underpowered. We believe our results provide evidence for the former, as HRs for heart failure and death with galectin-3, analyzed both by quartiles and continuously, were consistently higher than 1 (positive association) in whites and less than 1 (suggesting a negative association) in blacks (Table 5), even in minimally adjusted demographic models (Table 6).

Similarly, while galectin-3 discriminated events among whites, it did not do so among blacks. Furthermore, post-hoc power analyses demonstrate that this analysis had sufficient

power (with an α of 0.05 and a β of 0.20), requiring only 290 black participants to demonstrate the same relative risk that was found in whites (e.g., HR of 1.7 for the composite outcome, per SD increase in log-transformed galectin-3). While there is a dearth of published data evaluating the impact of galectin-3 among black subjects, it is worth noting that one of the few reports suggesting a null association for galectin-3 and outcomes was the HF-Action study, which had a high proportion of black participants (31%).[11]

We believe that our results highlight the importance of evaluating novel biomarkers in racially and ethnically diverse samples in order to ensure sufficient generalizability of the findings from biomarker research to the clinic. This is particularly important for heart failure biomarkers, given the increased risk and burden of heart failure in blacks compared to whites.[23] Specifically, while estimates differ by heart failure definition, geography, and secular trends, heart failure incidence rates are typically higher in blacks than in whites.[24] For example, in ARIC, the age-standardized incidence of acute decompensated heart failure among adults over 55 years differs significantly by race (10.9 in whites versus 14.3 in blacks, per 1000 person-years, $P<0.05$).[25] Relevant to these racial differences, our results suggest that, rather than just simply representing a noncausal marker of heart-failure physiology (galectin-3 is in fact thought to mediate heart failure through the development of fibrosis[3,26]), the biologic processes by which galectin-3 mediates heart failure may differ by race. While, for example, racial differences are also known to exist in heart-failure phenotype and response to therapy,[27] we are not aware of any research evaluating racial differences in galectin-3-mediated cardiac fibrosis and remodeling. Further research is warranted to address this question.

Our analysis has some limitations to consider. Our observational results are hypothesis generating and, due to limitations in power, we cannot rule out weaker adverse associations in blacks. Thus, larger studies are needed to validate our results. Similarly, overfitting of the fully adjusted model is a potential concern among the black subsample. However, in parsimonious demographic models, inclusive of just 3 adjusted covariates (Table 6), the associations between galectin-3 and events were similarly null (all HRs <1) among blacks. Furthermore, ICD diagnosis codes may not capture the true impact of galectin-3 on heart failure and we cannot discern between heart failure subtypes. In addition, while CARMRI preferentially selected subjects with carotid atherosclerosis, we used sampling weights to adjust our analyses, allowing generalization to the entire ARIC study sample. Finally, we do not have brain natriuretic peptide, N-terminal pro-brain natriuretic peptide, or other biomarker data available from the ARIC CARMRI study visit (so we cannot adjust for these additional markers in our analysis of galectin-3 drawn at this time point) and we also only have only 1 measurement of galectin-3 (repeat testing may better capture the utility of this biomarker[28]). Strengths include the rigorous collection of covariate data and active surveillance in ARIC, a diverse multicenter community-based sample.

In conclusion, galectin-3 is associated with heart failure and death in whites, but does not appear to be associated with either outcome in blacks. There is evidence of statistical interaction based on race status and, given that galectin-3 is thought to directly mediate heart failure (rather than just representing a noncausal biomarker), our results suggest that the processes by which galectin-3 mediates disease may differ by race. Further research is necessary to confirm this important finding.

Acknowledgments

The authors thank the staff and participants of the ARIC study for their important contributions. Dr McEvoy is supported by Johns Hopkins Division of Cardiology Magic the Matters Award and the Schafer fund for early career investigators.

Sources of Funding

This work was supported by a grant from the American Heart Association to Dr Selvin. The Atherosclerosis Risk in Communities (ARIC) Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). The ARIC carotid MRI examination was funded by U01HL075572-01.

Disclosures

Dr R. H. Christenson reports being a paid consultant for BG Medicine and that BG Medicine donated reagents for the galectin-3 measurements used in this analysis. All other coauthors report no relevant conflicts.

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Online Supplement

McEvoy et al. Galectin 3 and risk of Heart Failure and Death in Blacks and Whites

Supplemental eTable 1- Study population for incident heart failure and all-cause mortality (Main analysis)

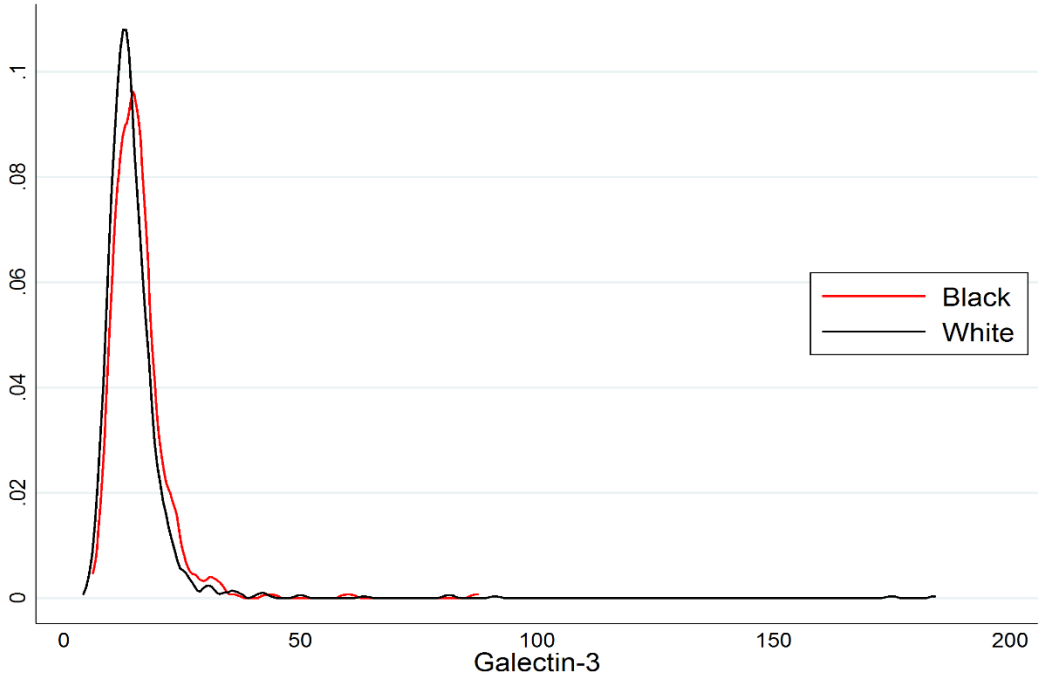
Exclusion Process	Exclusion	Population
Attended the carotid MRI (CARMRI) visit in 2004-2005		2,005
Prevalent heart failure	122	1,883
Missing model covariates or follow-up information	74	1,809
Population for incident HF and all-cause mortality: Analytic Study Sample		**1,809**

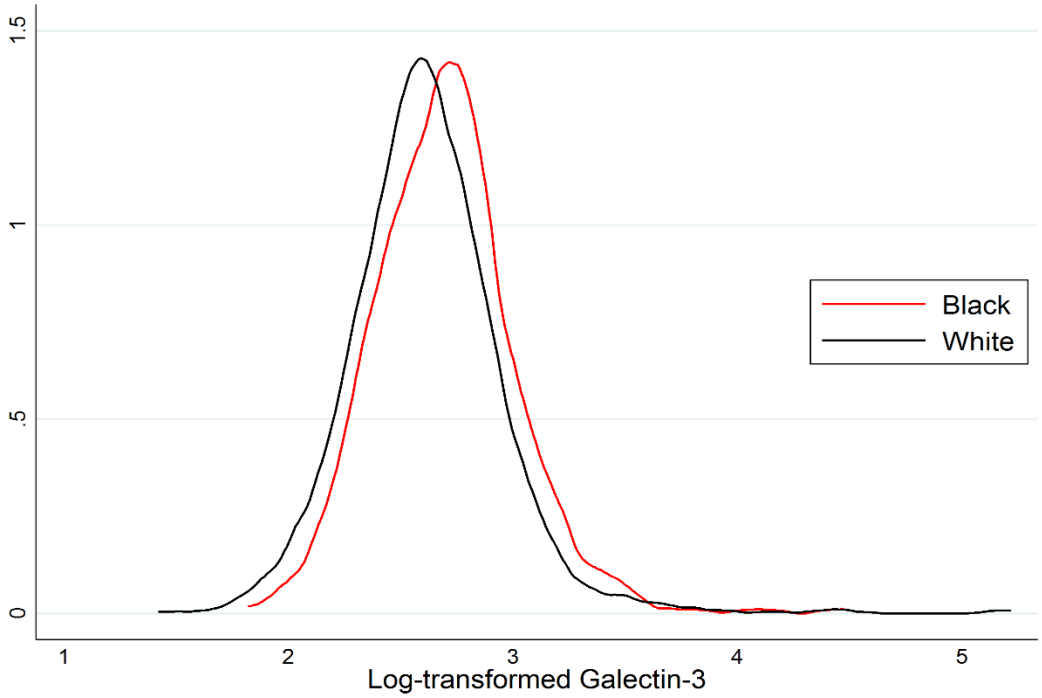
Supplemental eTable 2- Sensitivity analysis – fully adjusted Hazard Ratios for heart failure and all-cause mortality by Galectin-3 quartiles at baseline (N=1,809), with and without further adjustment for baseline Cardiovascular Disease status

Galectin-3, ng/mL		**Fully adjusted Model**		**Further adjusted for CVD**	
	Events (n)	HR	p-value	HR	p-value
Heart failure					
Quartile 1 (4.2-11.4)	27	1 (ref)	.	1 (ref)	.
Quartile 2 (11.4-13.8)	35	1.38 (0.74-2.56)	0.315	1.41 (0.75-2.63)	0.282
Quartile 3 (13.8-16.7)	40	1.12 (0.57-2.22)	0.735	1.16 (0.59-2.27)	0.661
Quartile 4 (16.7-184.1)	65	1.50 (0.75-3.01)	0.252	1.55 (0.76-3.14)	0.226
p-value for trend		*0.369*		*0.336*	
All-cause mortality					
Quartile 1 (4.2-11.4)	37	1 (ref)	.	1 (ref)	.
Quartile 2 (11.4-13.8)	43	0.85 (0.49-1.48)	0.571	0.87 (0.50-1.52)	0.631
Quartile 3 (13.8-16.7)	45	0.74 (0.42-1.31)	0.304	0.77 (0.44-1.35)	0.360
Quartile 4 (16.7-184.1)	87	1.32 (0.74-2.35)	0.346	1.36 (0.77-2.43)	0.294
p-value for trend		*0.409*		*0.360*	

Fully adjusted (Model 2): adjusted for age (years), race-center (whites-Washington County; whites-Minneapolis; blacks-Jackson; blacks-Forsyth County, whites-Forsyth County), sex (male or female), smoking status (current, former, or never), mean systolic blood pressure (mm Hg), mean diabolic blood pressure (mm Hg), anti-hypertensive medication use (yes or no), total cholesterol (mg/dL), HDL-cholesterol (mg/dL), diabetes status (self-reported history, medication use, glucose, HbA1c), and low eGFR (yes or no).

Supplemental eFigure-1. Untransformed and log-transformed distributions of galectin-3, by race status (Kernel density plots).





Y axis=Density, X axis=Galectin-3 in ng/mL (untransformed and log-transformed)