Clinical Trial

Plasma Galectin-3 and Heart Failure Outcomes in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy)

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ABSTRACT

Background: Elevated circulating levels of the protein galectin-3, a mediator of fibrogenesis, have previously been associated with adverse outcomes in heart failure (HF) patients and appear to modify response to certain pharmacologic therapies. This study investigated the relationship between galectin-3 level and clinical outcomes in HF patients randomized to implantable cardioverter defibrillator (ICD-only) or cardiac resynchronization therapy (CRT-D).

Methods and Results: Plasma galectin-3 concentrations were measured in 654 New York Heart Association functional class I/II patients participating in the MADIT-CRT trial. A heterogeneity of response was detected between pre-implantation galectin-3 and randomization group (CRT-D or ICD-only) on the primary MADIT-CRT trial end point of nonfatal HF event or death ($P = .045$). Among patients with baseline galectin-3 levels in the top quartile of the distribution, CRT-D was associated with a 65% reduction in risk of the primary end point (hazard ratio [HR] 0.35, 95% confidence interval [CI] 0.19−0.67), whereas among patients with lower baseline galectin-3 values CRT-D was associated with a 25% decrease in risk (HR 0.75, 95% CI. 0.51−1.11). Baseline galectin-3 level also was observed to be an independent predictor of the primary end point (multivariable adjusted HR per log unit increase: 1.55; 95% CI 1.01−2.38; $P = .043$).

Conclusions: Elevated galectin-3 was found to be an independent predictor of adverse HF outcome in patients with mildly symptomatic HF. A significant interaction of device randomization group with pre-implantation galectin-3 level was detected, with HF patients with the highest baseline galectin-3 levels deriving a disproportionately larger benefit from CRT-D. (*J Cardiac Fail 2014;20:793−799*)

Key Words: Prognosis, cardiac resynchronization therapy, biomarkers, patient selection.

Galectin-3 is a soluble beta-galactoside−binding lectin that has regulatory roles in fibrogenesis, inflammation, and tissue repair.[1−5] In a rat pericardial infusion model, galectin-3 was shown to promote cardiac fibrosis, fibroblast proliferation, collagen production, hypertrophy, and dysfunction.[6,7] Increased circulating galectin-3 levels may, therefore, reflect active and excessive myocardial fibrogenesis in patients with heart failure (HF). Several recent studies have reported an association between elevated circulating galectin-3 with cardiac ventricular remodeling as well as adverse clinical outcomes in patients with HF.[8−12] Patients with elevated baseline galectin-3 were also observed to be less likely to respond to statin therapy in a retrospective analysis of the Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA), and to angiotensin II receptor antagonist therapy in a retrospective analysis of the Valsartan Heart Failure Trial (ValHeFT).[13,14]

Multiple large randomized trials have demonstrated the benefit of implantable cardioverter defibrillators (ICDs)

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with cardiac resynchronization therapy (CRT-D) in reducing morbidity and mortality in HF and in improving left ventricular geometry.[15–19] Although active myocardial fibrosis and inflammation are thought to play important roles in ventricular remodeling in HF, the extent to which the benefit of CRT-D may relate to baseline fibrogenesis is unknown.

In the present study, we examined the relationship among plasma galectin-3 concentration, CRT-D, and clinical outcome in a large subset of patients with HF who participated in the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT).

Methods

Study Population

The design and primary results of MADIT-CRT have been reported previously.[17,20] In brief, MADIT-CRT was a multicenter, controlled, parallel-group study, with an imbalanced randomization (3:2, CRT with ICD or ICD-only, respectively), that was conducted in the United States (88 sites), Canada (2 sites), and Europe (20 sites). A total of 1,820 HF patients were enrolled with ejection fractions ≤30%, an ischemic etiology and New York Heart Association (NYHA) functional class I or II symptoms, or a nonischemic etiology and NYHA functional class II symptoms, and QRS durations ≥130 ms.

The present substudy included eligible subjects recruited in the United States from whom blood was drawn. Analyses performed as part of this substudy were prespecified in a prospectively defined analysis plan before the measurement of specimens. Specimens permitted by individual center Institutional Review Board (IRB) approval and patient consent to unspecified and/or unrestricted research use (including time limits) were eligible for galectin-3 measurement. A total of 654 galectin-3 measurements at baseline were available. Repeated galectin-3 measurements at 12 months after baseline were available for 394 patients. This investigation conformed with the principles outlined in the Declaration of Helsinki.

Determination of Biomarkers

Whole blood (EDTA) was shipped on the day of collection, at room temperature, to a core laboratory for plasma processing and storage at −80°C. Galectin-3 concentrations were determined from the banked specimens (thawed once) with the use of a commercial enzyme-linked immunosorbent assay (BG Medicine, Waltham, Massachusetts). All laboratory personnel conducting measurements on specimens were blinded to any patient-level data. B-Type natriuretic peptide (BNP) measurements were performed for MADIT-CRT by a core laboratory with the use of the Advia Centaur BNP Assay (Bayer Diagnostics, Tarrytown, New York).

Study Outcomes and Definitions

The prespecified primary end point of this substudy was the same as for the overall MADIT-CRT, namely, nonfatal HF event or death from any cause, whichever occurred first. End point adjudication was performed by independent blinded mortality and HF committees, as described previously.[20] The prespecified primary objective of this substudy was to determine whether subgroups of subjects defined by baseline galectin-3 level differed in magnitude of hazard of the primary end point associated with CRT-D compared with ICD-only therapy.

Statistical Analysis

Baseline characteristics were compared across galectin-3 quartiles with the use of the Cochran-Armitage trend test for categoric variables and the Spearman rank correlation test for continuous variables. Reported pairwise correlation coefficients are Spearman correlation coefficients.

Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) associated with treatment group and indicated end points. For categorization of the baseline galectin-3 variable, restricted cubic spline analysis was used to formally test the linearity of the relationship between baseline galectin-3 value and the log-hazard of the primary end point with the use of the methodology of Harrell,[21] and this test indicated a significant nonlinear relationship ($P = .003$; Supplemental Fig. 2). The detected nonlinearity occurred at the 4th quartile of the galectin-3 distribution (Supplemental Fig. 2), and as such the galectin-3 variable was dichotomized using that value of the distribution as the categorization boundary (43.3 ng/mL in the present study).[22]

Evaluation of the interaction test for treatment group by baseline galectin-3 category in a Cox regression model was performed by introducing coded variables for treatment group and categorized galectin-3 value, together with the interaction term. Event rates were analyzed with the use of Poisson regression. Evaluation of changes from baseline to 12 months in variables was performed with the use of analysis of covariance regression with the baseline variable value as a covariate. Multivariable Cox regression models comprised covariates individually associated with the primary end point. In Cox regression analyses, Martingale residuals were inspected for satisfaction of the linearity assumption of the Cox regression models. The independence of censoring times and event was tested by the method of Sun and Lee,[23] and no evidence of dependence between censoring times and event was detected at a 5% significance level. Risk reclassification was assessed at 18 months with the use of the metric of noncategoric continuous net reclassification improvement (NRI), with the base model comprising all covariates in a multivariable Cox regression model and the enhanced model additionally incorporating galectin-3 as a natural logarithmically transformed variable.[24] c-Statistics for areas under receiver operating characteristic curves were compared with the use of the method of deLong et al., which accounts for the correlated nature of the curves.[25]

All P values are 2 tailed. All analyses were performed with the use of SAS software, version 9.1 (SAS Institute, Cary, North Carolina), or R software, version 2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

Of the 1,820 subjects enrolled in MADIT-CRT, 654 (35.9%) had a baseline plasma specimen available for measurement of galectin-3. Of these 654 subjects, 386 were randomized to the CRT-D with ICD (CRT-D) group and 268 to the ICD-only group. There were no significant differences in baseline characteristics between the

MADIT-CRT patients with or without galectin-3 measurements (Supplemental Table 1). The clinical characteristics for all subjects with a baseline galectin-3 measurement, by quartiles of galectin-3 value, are presented in Table 1. Higher baseline galectin-3 levels were associated with larger left ventricular end-systolic volumes (LVESVs) and end-diastolic volumes (LVEDVs) at baseline, shorter 6-minute walk distance, higher serum creatinine, lower estimated glomerular filtration rate (eGFR), and higher B-type natriuretic peptide (BNP) levels. The prevalence of hypertension, smoking, and diabetes mellitus was similar across galectin-3 categories. Baseline galectin-3 levels were similar between the groups randomized to CRT-D versus ICD-only (mean 35.2 ± 15.8 ng/mL vs 35.0 ± 15.9 ng/mL, respectively; $P = .85$). Considered as a continuous measure, baseline galectin-3 was weakly correlated with baseline BNP (correlation coefficient $r = 0.17$; $P < .001$) and with serum creatinine ($r = 0.19$; $P < .001$) and eGFR ($r = -0.15$; $P < .001$).

Outcomes

Of the 654 subjects in the present substudy, the primary end point occurred in 143 subjects (21.9%) during follow-up. Among these primary events, 113 (79.0%) were first nonfatal HF events, and 30 (21.0%) were deaths. A total of 71 deaths occurred in the substudy. During follow-up, primary events occurred in 69 of the 386 subjects (17.9%) randomized to CRT-D and in 74 of the 268 subjects (27.6%) randomized to ICD-only.

Galectin-3, Randomization Group, and Outcomes

CRT-D efficacy in this substudy population was consistent with that of the overall MADIT-CRT (Fig. 1).[17] CRT-D was associated with a significantly lower hazard of primary event compared with ICD-only (unadjusted HR 0.61, 95% CI 0.44−0.84; $P = .003$). A formal interaction test detected a heterogeneity of CRT-D effect on the primary end point between high and low galectin-3 categories ($P = .045$ for interaction; $P = .027$ for interaction when adjusted for baseline BNP). Among patients with baseline galectin-3 in the high category, CRT-D was associated with a 65% reduction in risk of the primary end point (HR 0.35, 95% CI 0.19−0.67), and among patients with lower baseline galectin-3 value CRT-D was associated with a 25% decrease in risk (HR 0.75, 95% CI 0.51−1.11; Fig. 1). Correspondingly, the absolute reduction in primary event rate attributable to CRT-D, relative to ICD-only, in the high galectin-3 group was 11.2 fewer primary events per 100 patient-years ($P = .001$), and in the low galectin-3 group it was 2.1 fewer primary events per 100 patient-years ($P = .071$). Cumulative incidence curves for the primary end point by treatment category and by galectin-3 level among all subjects are shown in Fig. 2.

Table 1. Baseline Characteristics of Subjects by Baseline Galectin-3 Values

Characteristic	All Patients With Galectin-3 Values (n = 654)	Baseline Galectin-3				*P* Value for Trend
		Quartile 1 (n = 164)	Quartile 2 (n = 164)	Quartile 3 (n = 164)	Quartile 4 (n = 162)	
Age, y	64.9 (10.7)	64.0 (9.8)	64.9 (10.4)	65.9 (11.0)	64.4 (11.0)	.18
Female sex, n (%)	179 (27)	39 (24)	51 (31)	42 (26)	47 (29)	.51
Body-mass index, kg/m^2	29.1 (5.5)	28.8 (4.7)	28.9 (6.1)	29.1 (5.4)	29.4 (5.5)	.28
Systolic blood pressure, mm Hg	122.8 (17.6)	124.9 (17.4)	121.4 (16.8)	123.9 (19.5)	120.8 (16.4)	.63
NYHA II, n (%)	556 (85)	135 (82)	143 (87)	142 (87)	136 (84)	.73
LVEDV, mL	241.4 (60.5)	239.2 (71.3)	233.7 (51.5)	244.8 (59.3)	248.0 (57.9)	.008
LVESV, mL	172.5 (49.0)	172.1 (58.9)	165.5 (41.4)	175.5 (48.3)	176.9 (45.3)	.013
LVEF	0.29 (0.03)	0.29 (0.04)	0.30 (0.04)	0.29 (0.04)	0.29 (0.03)	.62
6-minute walk distance, m	356.0 (113.6)	385.7 (111.6)	347.1 (116.3)	335.5 (105.4)	355.8 (116.0)	.009
LBBB, n (%)	470 (72)	125 (76)	116 (71)	105 (64)	124 (77)	.71
Ischemic etiology, n (%)	336 (51)	78 (48)	89 (54)	96 (59)	73 (45)	.86
Current smoker, n (%)	76 (12)	23 (14)	16 (10)	19 (12)	18 (11)	.55
Medical history, n (%)						
Myocardial Infarction	258 (39)	62 (39)	67 (42)	73 (45)	56 (36)	.85
CABG	182 (28)	41 (25)	48 (29)	55 (36)	38 (24)	.98
Hypertension	421 (64)	96 (59)	104 (63)	116 (71)	105 (65)	.13
Diabetes mellitus	204 (31)	37 (23)	56 (34)	66 (40)	45 (28)	.19
Creatinine, mg/dL	1.2 (0.3)	1.0 (0.2)	1.2 (0.3)	1.2 (0.3)	1.2 (0.4)	.001
eGFR (mL min^{-1} 1.73 m^{-2})	68.0 (19.4)	75.0 (17.4)	67.3 (19.3)	64.9 (18.7)	64.7 (20.0)	.001
BNP), pmol/L, median (IQR	67 (27−148)	47 (20−101)	76 (29−144)	72 (34−182)	89 (35−176)	.012
Galectin-3, ng/mL, median (IQR)	31.4 (23.5−43.3)	20.0 (17.2−22.0)	27.1 (25.4−29.0)	36.7 (33.7−39.9)	53.6 (47.4−64.0)	na
Beta-blocker, n (%)	618 (94)	155 (95)	154 (94)	154 (94)	155 (96)	.66
ACE inhibitor, n (%)	505 (77)	129 (79)	120 (73)	128 (78)	128 (79)	.69
Aldosterone antagonist, n (%)	177 (27)	42 (26)	42 (26)	43 (26)	50 (31)	.29
ARB, n (%)	123 (19)	30 (18)	34 (21)	31 (19)	28 (17)	.72

Continuous variables are expressed as mean (SD). NYHA, New York Heart Association funcitonal class; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LBBB, left bundle branch block; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; IQR, interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; na = not applicable.

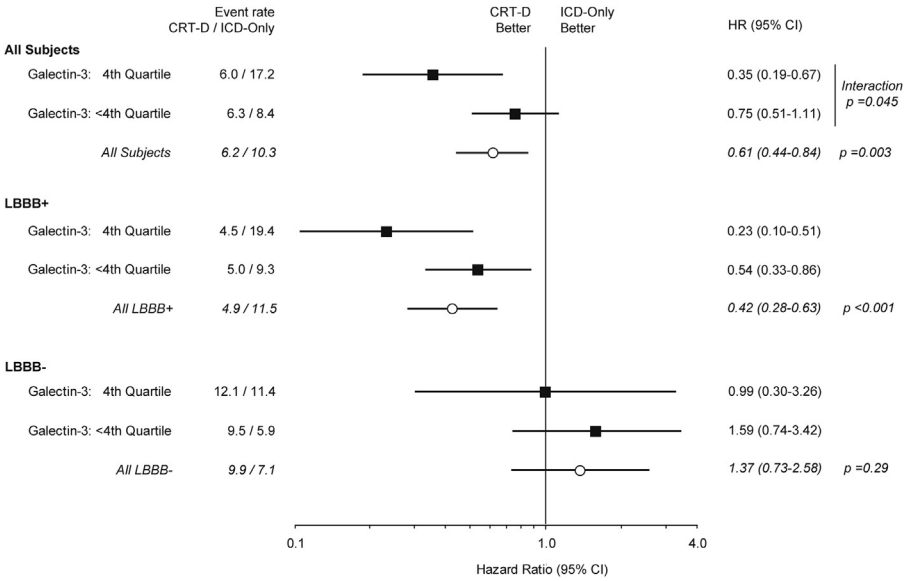

Fig. 1. Hazard ratio for primary end point (total mortality or nonfatal heart failure event) by baseline galectin-3 subgroup in all subjects, and by left bundle branch block (LBBB) status. Event rate indicates the number of primary events per 100 patient-years of follow-up. CRT-D, cardiac resynchronization therapy with implantable cardioverter-defibrillator; ICD, implantable cardioverter-defibrillator; HR, hazard ratio; CI, confidence interval.

Left bundle branch block (LBBB) identified patients most likely to benefit from CRT-D, as it did in the overall MADIT-CRT (Fig. 1). Among those within the high baseline galectin-3 category, CRT-D was associated with 14.9 fewer primary events per 100 patient-years ($P < .001$), and among patients in the lower galectin-3 category CRT-D was associated with 4.3 fewer primary events per 100 patient-years ($P = .011$). Among only patients with LBBB, a similar heterogeneity of treatment effect was observed as in the overall substudy ($P = .072$ for interaction; $P = .029$ for interaction when adjusted for baseline BNP), with patients in the higher galectin-3 category characterized by greater treatment benefit (Fig. 1).

Baseline galectin-3 level was a significant and independent predictor of mortality and morbidity in the overall substudy cohort (Table 2). In unadjusted Cox proportional hazards analysis of the primary end point, galectin-3 was significantly associated with increased hazard of the primary end point (HR per log unit increase: 1.64; 95% CI 1.13−2.40; $P = .010$). In a multivariable model adjusted for baseline clinical, cardiac, and demographic parameters (LVEF, hypertension, NYHA functional class, serum creatinine, diabetes, BNP, smoking status, randomization group, age, and sex), baseline galectin-3 remained significantly associated with the primary end point (HR per log unit increase: 1.55; 95% CI 1.01−2.38; $P = .043$). Addition of baseline galectin-3 resulted in moderate net positive reclassification of risk (continuous NRI: +17%; 95% CI −6% to +40%) and improvement in the c-statistic (from 0.72 to 0.75; $P = .032$). On detection of a significant interaction with treatment randomization group, the association of galectin-3 with outcome was investigated separately in the CRT-D and ICD-only groups. Elevated baseline pre-implantation galectin-3 was significantly associated with the primary outcome in the ICD-only group in a fully adjusted model, whereas among patients receiving CRT-D a similar association with outcome was absent (Table 2).

Serial Galectin-3 Measurements

Of the 654 subjects with a baseline galectin-3 measurement, 394 (60.2%) also had a galectin-3 measurement 12 months later. Fifteen subjects (2.3%) died within the first 12 months. Patients who had 12-month galectin-3 measurements did not differ from those who did not have a 12-month galectin-3 measurement in the baseline characteristics of Table 1, and no heterogeneity of treatment effect was detected based on whether or not a 12-month galectin-3 measurement was available ($P = .40$ for interaction on primary end point). Overall, there was a 1.3 ng/mL increase in mean galectin-3 levels over 12 months across all subjects and both randomization groups ($P = .054$ for change in galectin-3 level), and this change was independent from randomization group ($P = .36$). The increase in galectin-3 levels over 12 months was dependent on whether or not a primary event occurred during the interval ($P = .003$): subjects who experienced an event exhibited on average a 27.7% increase in galectin-3 level between baseline and 12 months (corresponding to a mean 6.8 ng/mL increase; $P = .016$), whereas subjects who did not experience an event in the first 12 months exhibited no significant change in galectin-3 level over that time period ($P = .20$).

Discussion

This substudy of MADIT-CRT investigated plasma galectin-3 levels in patients who were asymptomatic or

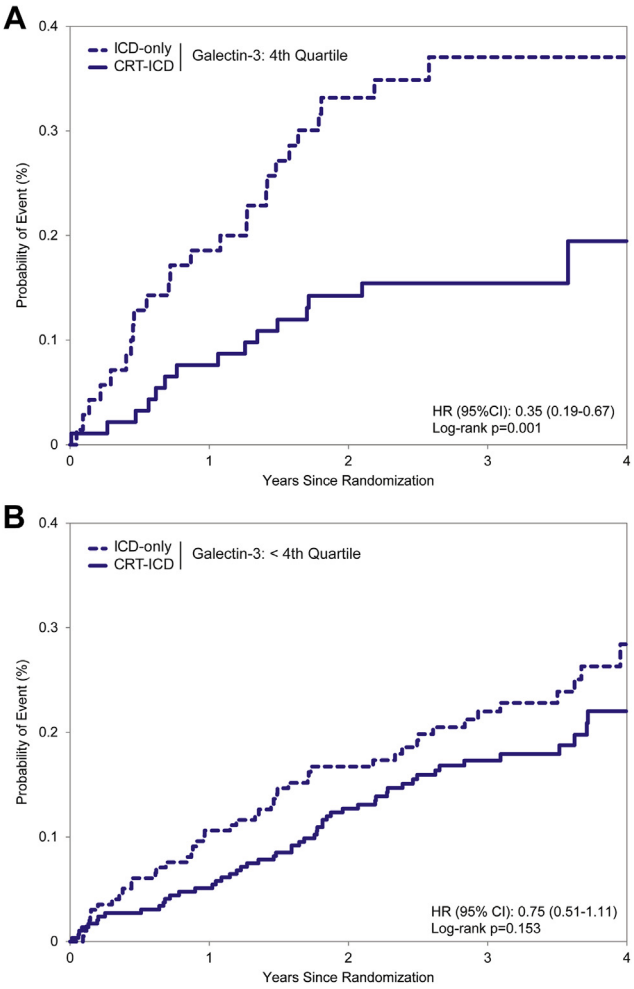

Fig. 2. Cumulative incidence of primary end point by treatment group in (A) the high (4th quartile) baseline galectin-3 group and (B) the lower galectin-3 group (<4th quartile). Log-rank test *P* values are as indicated in lower right of each figure. *P* = .045 for interaction between treatment group and baseline galectin-3 group. Abbreviations as in Fig. 1.

exhibiting mild HF symptoms (NYHA I/II) and were randomized to CRT-D or ICD-only device therapy. We observed that HF patients with the highest galectin-3 levels before CRT-D implantation derived a disproportionately larger benefit from CRT-D, evidenced by a statistical interaction indicating heterogeneity of CRT-D response by baseline galectin-3 level. In addition, consistently with results from more severe HF cohorts, elevated baseline galectin-3 levels were seen to be an independent predictor of adverse HF outcomes on adjustment for BNP, creatinine, LVEF, hypertension, NYHA functional class, diabetes, smoking status, age, and sex. We further observed that the association between baseline galectin-3 and adverse HF outcome risk was significantly attenuated among patients randomized to CRT-D in contrast to patients randomized to ICD-only, in which a significant and independent association persisted.

In earlier clinical and experimental studies, circulating levels of the protein galectin-3 were shown to be associated with active myocardial fibrogenesis, extracellular matrix collagen production, and ventricular remodeling.[3,5,7,11,12] Lok et al, in a serial echocardiography study of 182 HF patients, reported that baseline plasma galectin-3 level was among the most significant and independent predictors of LVEDV changes over a 4-month period.[11] Similarly, Kortekaas et al recently reported on a serial echocardiographic study after surgical mitral valve repair in HF and identified low baseline plasma galectin-3 concentration as the most significant predictor of left ventricular reverse remodeling, defined by change in LVESV over 6 months.[12]

In the context of predicting response to CRT-D in heart failure, relatively few studies have investigated the utility of plasma biomarkers in general, and of biomarkers of fibrogenesis and extracellular matrix metabolism in particular. In the Cardiac Resynchronization in Heart Failure (CARE-HF) trial, in which 813 patients with class III/IV HF were randomized to CRT-D or control, baseline levels of N-terminal pro-BNP (NT-proBNP) retained prognostic value in both CRT-D and control groups but were not found to predict response to CRT-D.[26] Several other serum biomarkers were also investigated in a smaller subset of 260 patients in the Cardiac Resynchronization in Heart Failure (CARE-HF) trial.[27] Galectin-3, NT-proBNP, N-terminal propeptide of type III procollagen, and matrix metalloproteinase 1 were associated with ≥1 outcomes, including all-cause mortality, death, or HF hospitalization, death from pump failure, sudden cardiac death, or death, or

Table 2. Association of Baseline Galectin-3 With Primary Outcome: Cox Proportional Hazards Regression Results

	Overall Cohort		ICD-Only		CRT-D	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Galectin-3 (per log unit increase)	1.64 (1.13−2.40)	.010	2.20 (1.31−3.68)	.003	1.22 (0.70−2.13)	.49
+ Age, sex	1.66 (1.13−2.44)	.009	2.18 (1.29−3.67)	.003	1.31 (0.74−2.31)	.35
+ Age, sex, LVEF, NYHA, diabetes status, smoking status, hypertension, BNP, serum creatinine*	1.55 (1.01−2.38)	.043	2.33 (1.25−4.34)	.008	1.24 (0.66−2.35)	.50

All covariates evaluated at baseline. ICD, implantable cardioverter-defibrillator; CRT-D, cardiac resynchronization therapy with ICD; HR, hazard ratio; CI, confidence interval; other abbreviations as in Table 1.

*Analysis for overall cohort is also adjusted for treatment randomization group (CRT-D or ICD-only).

LVEF ≤35%, independently from randomization group. However no statistically significant interaction was found between any of the tested biomarkers and response to CRT-D in that study. In an analysis of data from MADIT-CRT, baseline LVEF was not found to modify the clinical benefit of CRT-D.[28] In contrast, observational studies have reported associations between elevated baseline levels of collagen metabolism and positive response to CRT-D. Garcia-Bolao et al, in 2 study cohorts, observed that elevated baseline plasma levels of collagen type I carboxy-terminal propeptide, a marker of collagen synthesis and fibrogenesis, predicted response to CRT-D, defined by reduced cardiac mortality and functional improvement.[29,30]

The present study is the largest to date to investigate the relationship of baseline circulating galectin-3 to CRT-D outcomes. The observation of elevated baseline levels of galectin-3 among a subset of MADIT-CRT HF subjects is consistent with the concept of persistent myofibroblast activation and proliferation characterizing certain HF patients.[31,32] Such persistent myocardial fibrogenic metabolism is believed to play a detrimental role in pathologic fibrosis, resulting in maladaptive cardiac remodeling, myocardial stiffness, and worsening HF.[33]

The observation that patients with elevated pre-implantation levels of galectin-3 derived disproportionately greater benefit from CRT-D in the present study is consistent also with earlier studies reporting analogous findings with elevated collagen synthesis serum markers and CRT-D response.[29,30] Evidence from myocardial biopsies in HF patients indicates that cardiac resynchronization therapy, in addition to improving intraventricular dyssynchrony and functional and echocardiographic parameters, induces significant reverse remodeling at the cellular level, characterized by decreased myocyte size, reduced interstitial collagen content, and reduced cellular production of proinflammatory cytokines, such as tumor necrosis factor α.[34,35] Our results may indicate that metabolically active myocardial fibrogenesis may be present in a subset of class I/II HF patients with LV dyssynchrony, reflected in elevated levels of circulating galectin-3, and that these patients may derive disproportionate benefit from the antifibrotic and reverse myocardial remodeling effects of CRT-D. We observed in this study of NYHA functional class I and II HF patients that CRT-D implantation significantly attenuated the association of elevated galectin-3 with nonfatal HF event and death, a result not observed in the ICD-only group. Moreover, the significant increases in galectin-3 levels over 12 months were seen predominantly among patients experiencing adverse outcomes, further supporting the hypothesis that CRT-D may ameliorate persistent fibrogenesis and active collagen metabolism at a fundamental cellular and molecular level in the myocardium of failing hearts.

Study Limitations

Although MADIT-CRT was a multinational study, blood samples were collected in the United States only, and galectin-3 was measured only in samples from which individual center IRB approval and patient consent for unrestricted research was obtained. This limited the sample size. The present study was a retrospective analysis of specimens and associated data from a completed trial. In this study, samples were drawn at the clinical sites and shipped, on the day of collection, to the core lab as whole blood at room temperature. The protein galectin-3 has been demonstrated to be stable for up to 22 days at room temperature (22°C−28°C), and prolonged storage of whole blood for >8 hours has been associated with stable but finite leakage of intracellular galectin-3 and other proteins in specimens handled in this manner.[36−38] As such, the absolute levels of galectin-3 reported in this work may be elevated relative to those reported elsewhere. Despite an inability to combine and compare absolute values across studies, our findings are based on relative concentrations, and are consistent with the outcome of other HF studies and CRT-D trials.[8,10,27]

Conclusion

Elevated galectin-3 was found to be a significant and independent predictor of adverse HF outcome in patients with mildly symptomatic HF. In the present study, patients with galectin-3 values in the highest quartile also derived a disproportionately larger benefit from CRT-D. These data suggest that galectin-3 might identify the highest-risk patients who may derive the greatest absolute benefit from CRT-D, and prospective confirmatory trials to that end may be warranted.

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Disclosures

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Supplemental Data

Supplemental data related to this article can be found at http://dx.doi.org/10.1016/j.cardfail.2014.07.018.

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