

Galectin-3 and the Development of Heart Failure after Acute Coronary Syndrome: Pilot Experience from PROVE IT-TIMI 22

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BACKGROUND: Galectin-3 is a β -galactoside-binding lectin that has been implicated in cardiac fibrosis and remodeling, is increased in models of failure-prone hearts, and has prognostic value in patients with heart failure (HF). The relationship between galectin-3 and the development of HF after acute coronary syndrome (ACS) is unknown.

METHODS: In a nested case-control study among patients with ACS in PROVE IT-TIMI 22, we identified 100 cases with a hospitalization for new or worsening HF. Controls were matched (1:1) for age, sex, ACS type, and randomized treatment. Serum galectin-3 was measured at baseline (within 7 days post-ACS).

RESULTS: Patients who developed HF had higher baseline galectin-3 [median 16.7 $\mu\text{g/L}$ (25th, 75th percentile 14.0, 20.6) vs 14.6 $\mu\text{g/L}$ (12.0, 17.6), $P = 0.004$]. Patients with baseline galectin-3 above the median had an odds ratio of 2.1 (95% CI 1.2–3.6) for developing HF, $P = 0.010$. Galectin-3 showed a graded relationship with risk of HF. Cases were more likely to have hypertension, diabetes, prior MI, and prior HF; after adjustment for these factors, this graded relationship with galectin-3 quartile and HF remained significant [adjusted OR 1.4 (95% CI 1.1–1.9), $P = 0.020$]. When BNP was added to the model, the relationship between galectin-3 and HF was attenuated [adjusted OR 1.3 (95% CI: 0.96–1.9), $P = 0.08$].

CONCLUSIONS: The finding that galectin-3 is associated with the risk of developing HF following ACS adds to emerging evidence supporting galectin-3 as a bio-

marker of adverse remodeling contributing to HF as well as a potential therapeutic target.

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Galectin-3 is a soluble β -galactoside-binding lectin that appears to be a direct mediator of profibrotic pathways and is a potential marker of adverse cardiac remodeling. Galectin-3 is expressed by activated macrophages and induces cardiac fibroblasts to proliferate and deposit type I collagen in the myocardium (1). The expression of galectin-3 is substantially upregulated in animal models of heart failure (HF)⁴ and occurs before the development of overt clinical HF (1–3). The protein localizes to areas of fibrosis, suggesting an active role in modulation of the extracellular matrix (1). Moreover, intrapericardial infusion of galectin-3 in healthy and hypertensive rats leads to myocardial macrophage and mast cell infiltration, increased collagen I deposition, and impaired diastolic and systolic ventricular function (1, 4).

Given its apparent role in adverse cardiac remodeling, galectin-3 has been examined in patients with HF. In these patients, galectin-3 provides incremental prognostic value over traditional pressure-dependent biomarkers, such as B-type natriuretic peptide (BNP), and was recently cleared by the US Food and Drug Administration for the prognostic assessment of patients with chronic HF (5–11). Patients who develop acute coronary syndrome (ACS) have a significantly increased risk of developing subsequent HF, with substantial associated morbidity and mortality (12, 13). As such, there is strong clinical interest in identifying predictors of new HF in this population. Established clinical risk factors for HF after ACS, including age, de-

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⁴ Nonstandard abbreviations: HF, heart failure; BNP, B-type natriuretic peptide;

ACS, acute coronary syndrome; LVEF, left ventricular ejection fraction; PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22; MI, myocardial infarction; pO₂, oxygen pressure; OR, odds ratio; TGF, transforming growth factor; PIIINP, type III amino-terminal propeptide of procollagen; MMP-2, matrix metalloproteinase 2; Ac-SDKP, N-acetyl-seryl-aspartyl-lysyl-proline; PRIDE, ProBNP Investigation of Dyspnea in the Emergency Department; DEAL-HF, Deventer-Alkmaar Heart Failure; NT-proBNP, N-terminal pro-BNP.

creased left ventricular ejection fraction (LVEF) from baseline, hypertension, diabetes, and previous myocardial infarction, do not account for all of the attributable risk (12–14). In light of its pathobiology and application in patients with HF, we hypothesized that galectin-3 might be useful for assessing the risk of HF in patients with ischemic heart disease. To test this hypothesis, we performed a nested case-control pilot study to determine whether galectin-3 is associated with the risk of developing new or worsening heart failure after ACS.

Methods

STUDY DESIGN

We performed this nested case-control study with prospectively collected samples and outcomes from the main biomarker substudy within the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial. The design and results of the main trial have been described (15). Patients with unstable angina or myocardial infarction (MI) were randomized to standard or intensive statin therapy with pravastatin 40 mg daily vs atorvastatin 80 mg daily and followed for a mean of 2 years. We identified 100 cases with a hospitalization for new or worsening HF along with 100 control subjects who were matched 1:1 for age, sex, presenting ACS type (unstable angina, non-ST-elevation MI, or ST-elevation MI), and randomized treatment. Hospitalization for new or worsening HF was categorized as hospitalization with a final diagnosis of heart failure supported by evidence of pulmonary congestion on a chest radiograph and fulfillment of 2 of the following 6 criteria: rales in the midlung that did not clear with coughing; LVEF <40%; mean pulmonary capillary wedge pressure \geq 18 mmHg and cardiac index \leq 2.2 L/min·m²; use of diuretics to treat pulmonary congestion in patients not previously taking diuretics or an increase in dose in patients taking diuretics chronically; need for intubation for hypoxia; and oxygen saturation <90% or oxygen pressure (pO₂) <60 mmHg. LVEF was recorded in the case report form when assessed as part of routine care.

LABORATORY TESTING

Whole blood was obtained from subjects via standard venipuncture, and serum was isolated within 60 min of sampling, shipped overnight refrigerated, and stored at –70 °C or colder until the time of testing. Galectin-3 was measured at enrollment (within 7 days post-ACS) using an ELISA (BG Medicine). This assay has a lower limit of detection of 1.13 μ g/L (ng/mL) and demonstrates no cross-reactivity with other galectins or collagens (16). Total imprecision of the assay at concentra-

tions of 17.6 μ g/L and 26.3 μ g/L is 5.1% and 4.2%, respectively. Prior studies have shown that galectin-3 concentrations are stable for at least 6 months when samples are stored at either –20 °C or –70 °C and remain stable through at least 6 freeze–thaw cycles over that time (16). B-type natriuretic peptide (BNP) was measured using the Advia Centaur (Siemens).

STATISTICAL ANALYSIS

Continuous variables were summarized as mean and SD if normally distributed and median with interquartile range if non-normally distributed. We compared baseline characteristics using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Owing to anticipated skewness of biomarker values, we used paired nonparametric testing to compare galectin-3 concentrations between cases and controls. Patients were both categorized based on quartiles of galectin-3 and dichotomized at the median. We used conditional logistic regression to assess the association between galectin-3 and new or worsening HF. To adjust for traditional risk factors for HF, including hypertension, diabetes, history of HF, prior MI, baseline BNP, and LVEF, we used multivariable conditional logistic regression. We assessed the correlation between galectin-3 and BNP and LVEF using Spearman rank correlation coefficient. Significance was set at a 2-sided *P* value <0.05. All statistical analyses were performed using STATA version 10.1.

Results

BASELINE CHARACTERISTICS

Baseline characteristics for cases and controls are shown in Table 1. Cases were more likely to have pre-existing hypertension, a history of HF, and prior MI. Cases were also more likely to have an increased baseline BNP concentrations and systolic dysfunction, defined as LVEF <40%.

GALECTIN-3 AND HEART FAILURE

Patients who developed HF had a higher baseline galectin-3 concentration [median 16.7 μ g/L (25th, 75th percentiles 14.0, 20.6)] vs controls [14.6 μ g/L (12.0, 17.6)], *P* = 0.004. Patients with baseline galectin-3 above the median were twice as likely to develop HF [odds ratio (OR) 2.1 (95% CI 1.2–3.6), *P* = 0.010]. Galectin-3 showed a graded relationship with the risk of heart failure, and patients in the highest galectin-3 quartile had a 3.6 times higher odds of developing HF than those in the baseline quartile (*P*_{trend} = 0.003) (Fig. 1).

After adjustment for clinical risk factors for HF, including hypertension, diabetes, prior HF, and prior MI, the significant graded relationship with HF per-

Table 1. Baseline characteristics of cases and controls.

Characteristic	Controls	Cases	P
n	100	100	
Mean age, years (SD)	65.7 (10.9)	65.7 (10.9)	1.0
Male, %	73	73	1.0
Hypertension, %	54	68	0.04
Diabetes, %	23	32	0.15
Prior congestive heart failure, %	5	21	0.001
Prior MI, %	25	39	0.03
ACE inhibitor/angiotensin receptor blocker, %	78	80	0.73
Beta-blocker, %	90	82	0.10
LVEF <40%	11 ^a	31 ^b	0.003
BNP >80 pg/mL, % ^c	20	41	0.002
Median peak creatine kinase MB, ng/mL (interquartile range)	6 (1–21) ^d	4 (1–14) ^e	0.43

^a n = 74 with LVEF available.
^b n = 65 with LVEF available.
^c n = 188 with both biomarkers available.
^d n = 72 with creatine kinase MB available.
^e n = 70 with creatine kinase MB available.

sisted across the quartiles of galectin-3 concentration, with adjusted OR 1.4 per quartile (95% CI 1.1–1.9, *P* = 0.020), and when modeled as a continuous variable demonstrated a 47% increase in the adjusted relative odds of HF for each SD increase in galectin-3 (*P* = 0.049). The adjusted OR of HF in patients with

galectin-3 concentration above the median was 1.9 (95% CI 1.0–3.5, *P* = 0.045). Moreover, in an analysis restricted to patients without a history of HF, the significant relationship between galectin-3 quartile and odds of HF remained, with an adjusted OR of 1.4 (95% CI 1.0–2.0, *P* = 0.038).

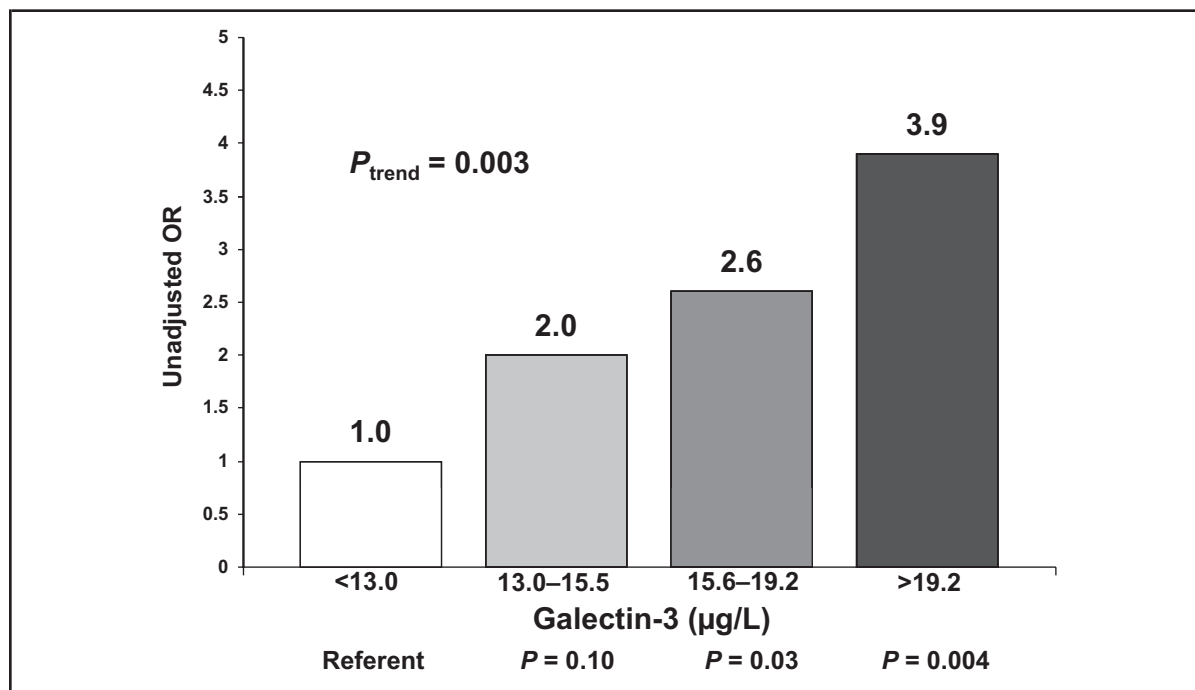


Fig. 1. Univariate unadjusted relative odds of heart failure by galectin-3 quartile.

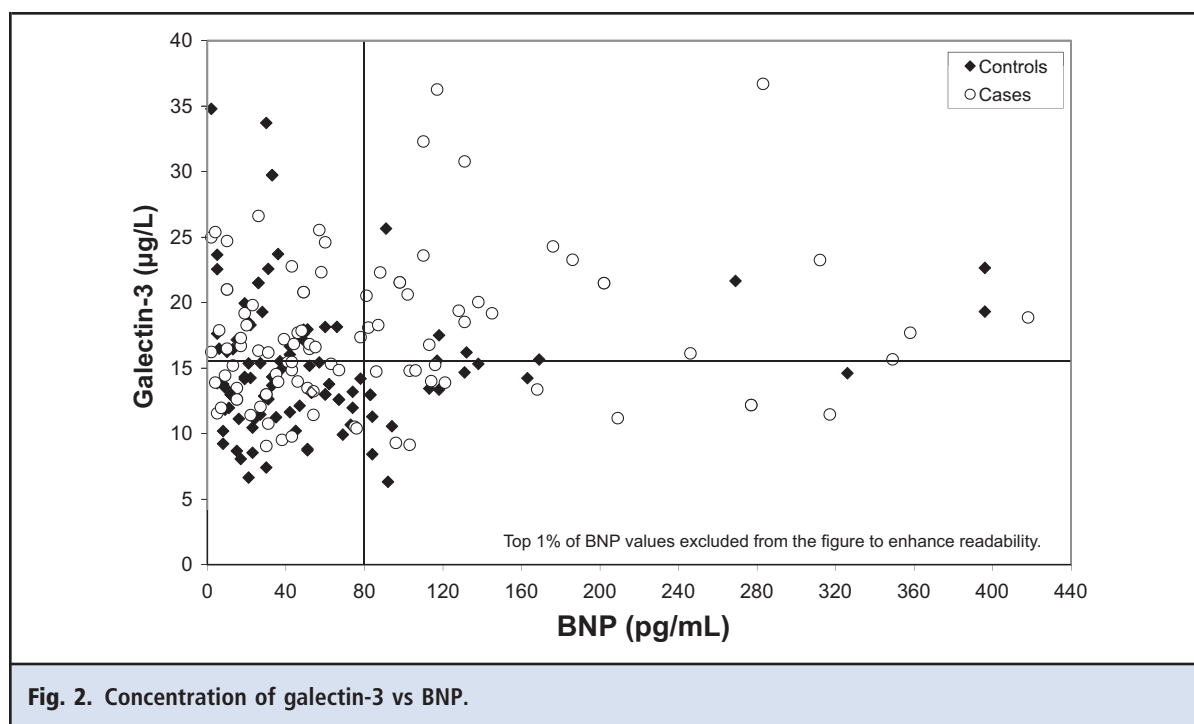


Fig. 2. Concentration of galectin-3 vs BNP.

EVALUATION WITH OTHER BIOMARKERS

Baseline BNP >80 pg/mL was also strongly associated with heart failure [OR 2.8 (95% CI 1.3–6.0), $P = 0.009$]. Galectin-3 did not significantly correlate with BNP (Spearman $\rho = 0.13$, $P = 0.08$) (Fig. 2). When both BNP and galectin-3 were included in the multivariable model, however, the graded relationship between galectin-3 and HF was attenuated [adjusted OR 1.3 (95% CI 0.96–1.9), $P = 0.08$]. When patients were stratified by both galectin-3 at the median and BNP at the cut point of 80 pg/mL, patients with increased galectin-3 and BNP had the highest odds of heart failure: OR 4.7 (95% CI 1.7–13.0; $P = 0.002$) for high BNP/high galectin-3 compared to the referent of low BNP/low galectin-3 (Fig. 3).

There was a weak but significant negative correlation between galectin-3 and LVEF (Spearman $\rho = -0.31$, $P = 0.0002$). When LVEF was added to the multivariable model, the relationship between galectin-3 and HF was attenuated [adjusted OR 1.4 (95% CI 0.9–2.3), $P = 0.15$].

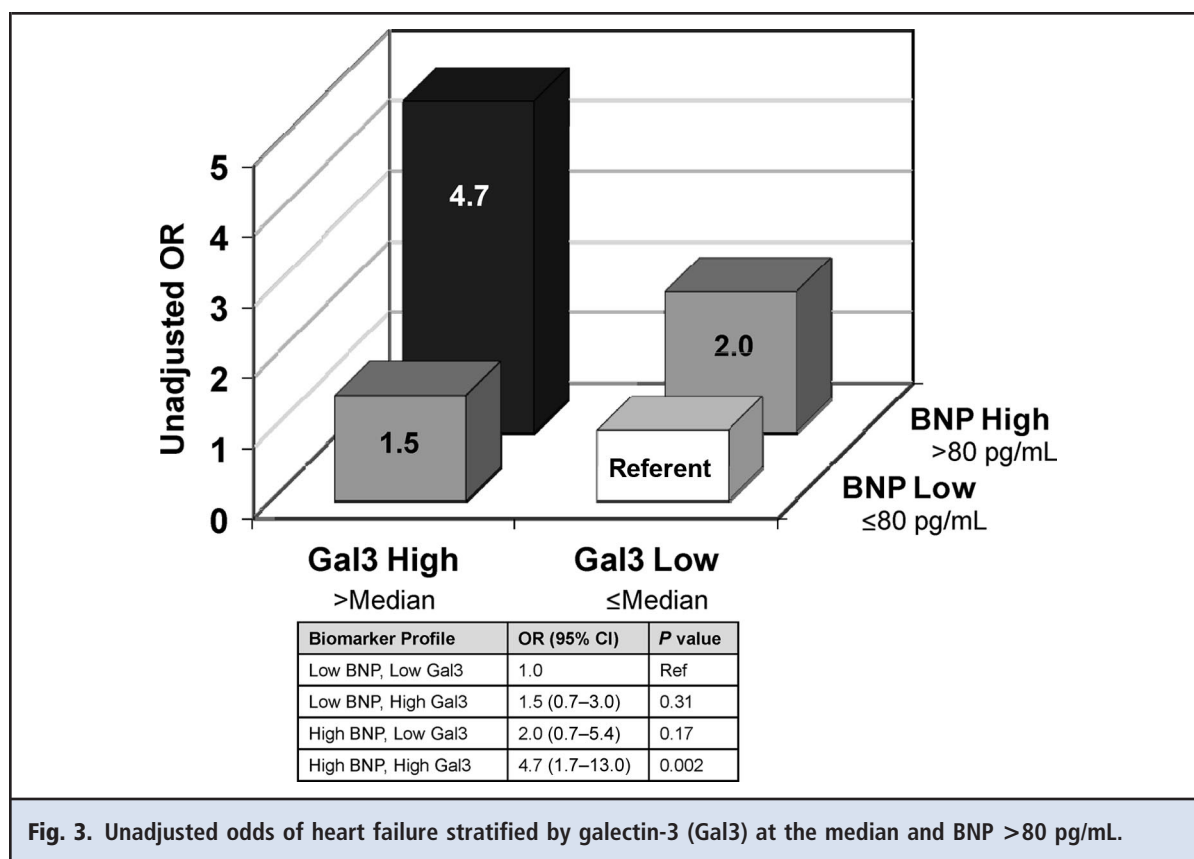
Discussion

The results of this pilot study suggest that the concentration of galectin-3 after ACS is associated with the risk of developing subsequent HF. The observed significant graded relationship supports the potential clinical relevance of galectin-3-mediated pathways in patients with ischemic heart disease who develop HF. Together

with experimental data, our pilot findings reinforce clinical interest in the active role that galectin-3 appears to play in promoting cardiac fibrosis and adverse remodeling. As a prognostic biomarker in patients with ACS, galectin-3 was associated with HF independently of clinical risk factors but was not as strongly associated as BNP in this small study population.

GALECTIN-3 AND THE PATHOBIOLOGY OF HF

Galectin-3 appears to link pathways of inflammation and fibrosis and may contribute to the development of HF by mediating progressive alteration of the myocardial extracellular matrix (17). Myocardial injury generates inflammatory signals that recruit activated macrophages to the myocardium. Mediators such as osteopontin stimulate these macrophages to secrete galectin-3 (3), which appears to act through upregulation of the transforming growth factor (TGF)- β /Smad3 signaling pathway, causing cardiac fibroblasts to proliferate and produce type I collagen, ultimately leading to an accumulation of myocardial collagen and impaired diastolic and systolic function (1, 4). In a mouse model of desmin-deficient HF, knocking out the gene for osteopontin resulted in dramatically decreased galectin-3 expression and subsequently less cardiac fibrosis and improved echocardiographic parameters of ventricular function (3). In patients with chronic HF, galectin-3 concentrations have been correlated with markers of extracellular matrix turnover, such as type III amino-terminal propeptide of procoll-



lagen (PIIINP) and matrix metalloproteinase 2 (MMP-2), implying a relationship between macrophage activation and collagen turnover (18). Intriguingly, *N*-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP), a monocyte-derived antiinflammatory and antifibrotic peptide that is degraded by ACE, inhibits galectin-3 expression in the left ventricle and reduces galectin-3-induced macrophage activation and migration (19). In a rat model, intrapericardial infusion of Ac-SDKP mitigated many of the adverse effects of galectin-3, leading to reduced myocardial macrophage and mast cell density, decreased left ventricular collagen burden, and improved diastolic and systolic function (4). These data suggest that the adverse consequences associated with galectin-3 may be modifiable.

Galectin-3 may be particularly important in patients with ischemic heart disease in whom there is sufficient inflammatory substrate for macrophage recruitment and subsequent galectin-3 secretion. In patients with advanced decompensated heart failure, increased galectin-3 concentrations were significantly correlated with an ischemic etiology of HF (10). Overall, our findings add to the evidence supporting the relevance of galectin-3 in patients with ischemic heart disease and the investigation of galectin-3-related pathways as a

potential target for therapeutic intervention. Given our observation that galectin-3 is related to the risk of HF after ACS, it is reasonable to hypothesize that therapies which impact adverse remodeling, such as ACE inhibitors or aldosterone receptor antagonists, might be particularly beneficial in patients with increased galectin-3 after ACS. This hypothesis requires investigation before such an application would be entertained for clinical use.

GALECTIN-3 AS A CLINICAL BIOMARKER

Galectin-3 has been validated as a biomarker with independent prognostic value in patients with both acute and chronic HF. Data from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study, which examined 599 patients presenting to the emergency room with acute dyspnea, demonstrated that among the 209 patients ultimately diagnosed with acute HF, baseline galectin-3 was a superior predictor of short-term (60-day) mortality than NT-proBNP and remained a significant predictor of long-term mortality at 4 years in a subset of patients (5, 6). In a group of patients with chronic, severe heart failure from the Deventer-Alkmaar Heart Failure Study (DEAL-HF), baseline galectin-3 was a significant pre-

dictor of long-term mortality (at 6.5 years) after correcting for age, sex, renal dysfunction, and N-terminal pro-BNP (NT-proBNP) (7). The prognostic value of galectin-3 for predicting survival has been further validated in 4 subsequent studies of patients with chronic HF (8, 11), and it may be particularly useful in patients with heart failure and preserved ejection fraction (8).

Our study broadens the potential role for galectin-3 as a prognostic biomarker in patients with established HF to those with acute ischemic heart disease at risk for future HF. Our observation of a relationship between galectin-3 and HF after ACS that was independent of clinical risk factors supports additional investigation of galectin-3 in this population. The absence of an incremental value over BNP may relate to the small sample size of our pilot study. Additional evaluation in larger studies would be needed to assess whether there is a useful clinical role for galectin-3 as a prognostic biomarker in patients with ischemic heart disease. However, the very weak pattern of correlation between galectin-3 and BNP argues against pure confounding by BNP and supports the experimental evidence that expression of these proteins is mediated by different biological pathways. Moreover, the finding that patients with elevation of both galectin-3 and BNP were at the highest risk for HF suggests potential incremental value from a strategy that uses both of these biomarkers for assessment of HF risk in patients post-ACS.

LIMITATIONS

There are limitations to this study. The sample size was relatively small, which limited our ability to adjust for a more comprehensive list of heart failure risk factors. LVEF was collected only according to local practice, which limited our ability to fully assess the relationship between galectin-3, LVEF, and HF. We cannot rule out confounding by LVEF and that galectin-3 is simply a marker of deteriorating LV function. However, the correlation between LVEF and galectin-3, while significant, was weak, and galectin-3 was often increased in the absence of systolic dysfunction. In addition, clinical studies have shown that galectin-3 concentration does not correlate well with indices of LV size and function and is more strongly correlated with echocardiographic parameters of impaired diastolic relaxation and RV dysfunction (6, 9). Galectin-3 is a ubiquitously expressed protein that has been implicated in fibrosis of other organs, including the kidneys, liver, pancreas, and lungs, and our study does not establish whether serum galectin-3 concentration correlates with cardiac galectin-3 expression or myocardial collagen burden (20–25). We used a prespecified clinical definition of heart failure based on objective criteria, but in this large

multinational clinical outcomes study, it was not feasible to require invasive evaluation of intracardiac pressures in all cases of suspected heart failure. Therefore, it is possible that in some patients other disease processes may have mimicked heart failure and contributed to elevation of galectin-3. However, based on our application of standardized criteria in this population with established ischemic heart disease, we expect any such contribution to have been small.

Conclusions

Our pilot study demonstrates that the serum concentration of galectin-3 is associated with the risk of developing HF after ACS and supports the potential clinical relevance of galectin-3–related pathways in patients with ischemic heart disease. Together with experimental data, our findings suggest that galectin-3 may merit consideration as a potential novel target for therapeutics to prevent HF in this population. Additional investigation is warranted to explore the mechanisms of this relationship in patients with ACS and to clarify whether there is sufficient incremental prognostic value to consider galectin-3 as part of a screening strategy to identify patients with ischemic heart disease who are at higher risk of developing HF after ACS.

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References

- Sharma UC, Pokharel S, van Brakel TJ, van Berlo JH, Cleutjens JPM, Schroen B, et al. Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. *Circulation* 2004;110:3121–8.
- Kamal AK, Watanabe K, Ma M, Abe Y, ElBarbary R, Kodama M, Aizawa Y. A novel phenylpyridazinone, T-3999, reduces the progression of autoimmune myocarditis to dilated cardiomyopathy. *Heart Vessels* 2011;26:81–90.
- Psarras S, Mavroidis M, Sanoudou D, Davos CH, Xanthou G, Varela AE, et al. Regulation of adverse remodelling by osteopontin in a genetic heart failure model. *Eur Heart J* [E-pub ahead of print 2011 Jul 20].
- Liu Y-H, D'Ambrosio M, Liao T-D, Peng H, Rhaleb NE, Sharma U, et al. *N*-acetyl-seryl-aspartyl-lysyl-proline prevents cardiac remodeling and dysfunction induced by galectin-3, a mammalian adhesion/growth-regulatory lectin. *Am J Physiol Heart Circ Physiol* 2009;296:H404–12.
- van Kimmenade RR, Januzzi JL, Ellinor PT, Sharma UC, Bakker JA, Low AF, et al. Utility of amino-terminal pro-brain natriuretic peptide, galectin-3, and apelin for the evaluation of patients with acute heart failure. *J Am Coll Cardiol* 2006;48:1217–24.
- Shah RV, Chen-Tournoux AA, Picard MH, van Kimmenade RR, and Januzzi JL. Galectin-3, cardiac structure and function, and long-term mortality in patients with acutely decompensated heart failure. *Eur J Heart Fail* 2010;12:826–32.
- Lok DJA, van Der Meer P, de la Porte PWB-A, Lipsic E, Wijngaarden JV, Hillege HL, van Veldhuisen DJ. Prognostic value of galectin-3, a novel biomarker of fibrosis, in patients with chronic heart failure: data from the DEAL-HF study. *Clin Res Cardiol* 2010;99:323–8.
- de Boer RA, Lok DJA, Jaarsma T, van Der Meer P, Voors AA, Hillege HL, van Veldhuisen DJ. Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction. *Ann Med* 2011;43:60–8.
- Tang WH, Shrestha K, Shao Z, Borowski AG, Troughton RW, Thomas JD, Klein AL. Usefulness of plasma galectin-3 levels in systolic heart failure to predict renal insufficiency and survival. *Am J Cardiol* 2011;108:385–90.
- Felker GM, Fiuzat M, Shaw LK, Donahue M, Adams KF, Zannad F, et al. Prognostic value of galectin-3 in chronic heart failure: results from the HF-ACTION study. *Eur Heart J* 2010;31(Suppl 1):429.
- Ueland T, Aukrust P, Broch K, Aakhus S, Skardal R, Muntendam P, Gullestad L. Galectin-3 in heart failure: high levels are associated with all-cause mortality. *Int J Cardiol* 2011;150:361–4.
- Lewis EF, Moye LA, Rouleau JL, Sacks FM, Arnold MO, Warnica JW, et al. Predictors of late development of heart failure in stable survivors of myocardial infarction: the CARE Study. *J Am Coll Cardiol* 2003;42:1446–53.
- Guidry UC, Evans JC, Larson MG, Wilson PW, Murabito JM, and Levy D. Temporal trends in event rates after q-wave myocardial infarction: the Framingham Heart Study. *Circulation* 1999;100:2054–9.
- Ali AS, Rybicki BA, Alam M, Wulbrecht N, Richer-Cornish K, Khaja F, et al. Clinical predictors of heart failure in patients with first acute myocardial infarction. *Am Heart J* 1999;138:1133–9.
- Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–504.
- Christenson RH, Duh S-H, Wu AH, Smith A, Abel G, deFilippi CR, et al. Multi-center determination of galectin-3 assay performance characteristics: anatomy of a novel assay for use in heart failure. *Clin Biochem* 2010;43:683–90.
- Henderson NC, Sethi T. The regulation of inflammation by galectin-3. *Immunol Rev* 2009;230:160–71.
- Lin YH, Lin LY, Wu YW, Chien KL, Lee CM, Hsu RB, et al. The relationship between serum galectin-3 and serum markers of cardiac extracellular matrix turnover in heart failure patients. *Clin Chim Acta* 2009;409:96–9.
- Sharma U, Rhaleb N-E, Pokharel S, Harding P, Rasoul S, Peng H, Carretero OA. Novel anti-inflammatory mechanisms *N*-acetyl-asp-lys-pro in hypertension induced target organ damage. *Am J Physiol Heart Circ Physiol* 2008;294:H1226–32.
- Henderson NC, Mackinnon AC, Farnworth SL, Kipari T, Haslett C, Iredale JP, et al. Galectin-3 expression and secretion links macrophages to the promotion of renal fibrosis. *Am J Pathol* 2008;172:288–98.
- Henderson NC, Mackinnon AC, Farnworth SL, Poirier F, Russo FP, Iredale JP, et al. Galectin-3 regulates myofibroblast activation and hepatic fibrosis. *Proc Natl Acad Sci U S A* 2006;103:5060–5.
- Hsu DK, Dowling CA, Jeng KC, Chen JT, Yang RY, Liu FT. Galectin-3 expression is induced in cirrhotic liver and hepatocellular carcinoma. *Int J Cancer* 1999;81:519–26.
- Wang L, Friess H, Zhu Z, Frigeri L, Zimmermann A, Korc M, et al. Galectin-1 and galectin-3 in chronic pancreatitis. *Lab Invest* 2000;80:1233–41.
- Nishi Y, Sano H, Kawashima T, Okada T, Kuroda T, Kikkawa K, et al. Role of galectin-3 in human pulmonary fibrosis. *Allergol Int* 2007;56:57–65.
- Kasper M, Hughes RC. Immunocytochemical evidence for modulation of galectin-3 (Mac-2), a carbohydrate binding protein, in pulmonary fibrosis. *J Pathol* 1996;179:309–16.