Utilization of Galectin-3 in Case Management Across the Spectrum of Heart Failure

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In patients with heart failure as a result of mechanical and neurohormonal derangements, macrophages secrete galectin-3, which is a paracrine and endocrine factor that stimulates additional macrophages, pericytes, myofibroblasts, and fibroblasts to proliferate and secrete procollagen I, which is irreversibly crosslinked to form fibrotic collagen. Normal plasma concentrations of galectin-3 are $<$ 11.0 ng/mL. Galectin-3 measured in blood has been shown to predict the development of all-cause mortality and heart failure in the general population, identify increased risk for de novo heart failure and progressive loss of renal filtration function in healthy middle-aged adults, predict cardiac failure in patients after acute coronary syndromes, help establish the diagnosis of heart failure with preserved ejection fraction in patients presenting with effort intolerance, and aid in the prognosis of both systolic and nonsystolic heart failure for the outcomes of hospitalization and death. This article presents case discussions of these applications to highlight the importance of galectin-3 measurement across the spectrum of patients at risk for cardiorenal disease.

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KEY WORDS

Galectin-3 • Heart failure • Chronic kidney disease • Biomarker • Medical management • Hospitalization • Mortality

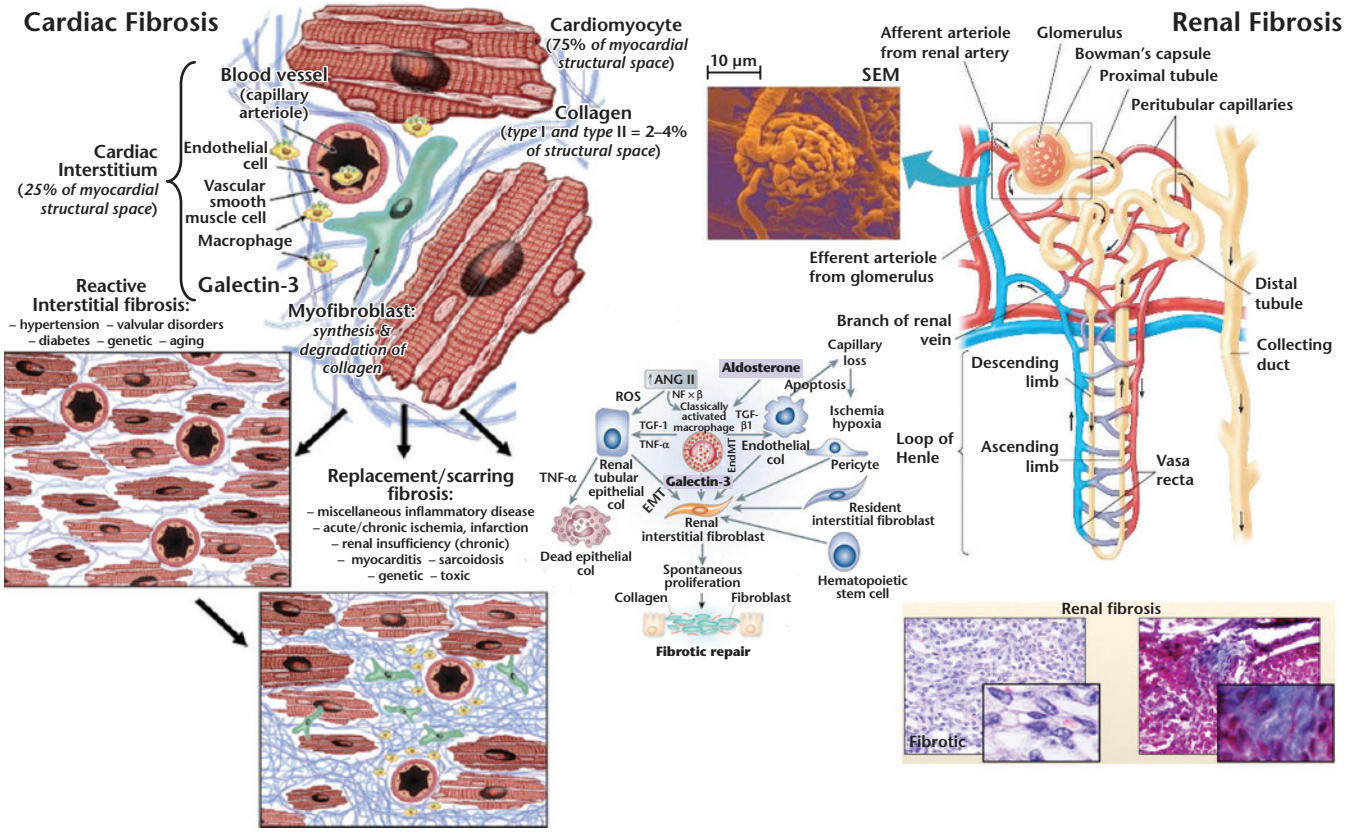
Both heart failure (HF) and kidney failure are common chronic comorbidities associated with older age and years of cardiometabolic disease. HF is a complex mechanical and neurohumoral syndrome manifested by hemodynamic congestion presenting with dyspnea, orthopnea, paroxysmal nocturnal dyspnea, or peripheral edema, coupled with objective evidence of cardiac dysfunction.[1,2] The functional and histopathologic correlates of cardiac failure include myocyte dysfunction, accelerated apoptosis, and replacement fibrosis.[3] In the failing human heart, considerable quantities of myocardium can be replaced with collagen and interstitial matrix proteins, leading to the clinical observations of both diastolic and systolic dysfunction. In addition, cardiovascular fibrosis leads to both vascular stiffness and ventricular dysfunction as pathways to pump failure (Figure 1). Heterogeneity of conduction in the myocardium as a result of fibrosis can lead to forms of conduction disturbances, dyssynchrony, and re-entrant arrhythmias, including ventricular tachycardia, which often degenerates to ventricular fibrillation and leads to sudden death. Thus, assessment of the process of cardiovascular fibrosis with a novel in vitro diagnostic assay in plasma can be viewed as a breakthrough in understanding complex cases along the spectrum of cardiac failure.

HF is a leading cause of emergency room visits, hospitalizations, and death with 5 million cases in the United States and another 500,000 diagnosed each year, resulting in the forecasted prevalence to double by year 2040.[4,5] Advancing age is a leading determinant of HF, and thus, the incidence of HF nearly doubles for patients $>$ 85 years compared with those $<$ 75 years.[4] Senescence contributes to tissue fibrosis and vascular stiffness, which are central to the pathogenesis of HF.

Approximately two-thirds of HF patients have ischemic cardiomyopathy with zones of cardiac fibrosis as a result of ischemia and infarction.[5,6] The extent of coronary artery disease and prior infarction is associated with the severity of left ventricular (LV) dysfunction.[7]

Nonischemic cardiomyopathy accounts for the remaining one-third of individuals with reduced LV ejection fraction (LVEF) and is associated with antecedent hypertension in a majority of cases. Most forms of nonischemic cardiomyopathy have an underlying genetic susceptibility (eg, polymorphisms in titin), and then a superimposed myocardial insult such as myocarditis, alcohol, cardiotoxic medication (eg, anthracyclines), infiltrative diseases (eg, sarcoid,

Figure 1. Pathogenic processes involved in both cardiac and renal fibrosis are dependent on tissue macrophages and the secretion of galectin-3.



amyloid), radiation, or autoimmune injury. The important aspect of the epidemiology of nonischemic cardiomyopathy is that, among those discovered to have idiopathic dilated cardiomyopathy, approximately 20% of first-degree family members have subclinical disease.[8] In cases of nonischemic cardiomyopathy, most have excess deposition of collagen in the extracellular matrix and tissue fibrosis present at necropsy.[9]

Chronic kidney disease (CKD) is commonly associated with HF, with the most common determinants being longstanding hypertension and type 2 diabetes. When HF induces a more rapid progression of CKD with loss of glomerular filtration function, then this is termed a chronic type 2 cardiorenal syndrome.[10] It has been recently appreciated that, similar to replacement fibrosis in the myocardium, loss of renal parenchyma and nephron units is supplanted by fibrosis, which is directed by macrophages secreting galectin-3. Because galectin-3 has been identified in large quantities in the kidney in the setting of experimental ureteral obstruction, it is possible that, in addition to the heart, the kidneys are a source of systemic levels of galectin-3 measured in blood.[11]

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Pathophysiology of Myocardial Fibrosis and Galectin-3

The participation of galectin-3 in cardiac fibrosis has been described in detail by McCullough and colleagues.[12] Responses to acute and chronic damage can involve recruitment of monocytes and macrophages to the myocardium, production of galectin-3 from local pericytes, mast cells, and macrophages, resulting in activation of resident fibroblasts and myofibroblasts, and in the final common pathway, increases in the secretion of procollagen into the extracellular matrix, which is irreversibly crosslinked to collagen-generating cardiac fibrosis (Figure 1).[13]

The galectin family of carbohydrate-binding proteins (15 in mammals and 11 in humans) are important participants in this process. Galectins are carbohydrate-binding proteins involved in the regulation of satellite cell signaling, immunity, and cancer. Galectin-3 is an approximately 30 kDa glycoprotein that has a carbohydrate-recognition-binding domain of approximately 130 amino acids that enable the binding of β-galactosides.[14-16] It is encoded by a single gene, *LGALS3*, located on chromosome 14, locus q21–q22, expressed in the nucleus and mitochondria.[17] Galectin-3 as a paracrine signal is involved in cell adhesion, activation, chemoattraction, growth and differentiation, cell cycle, and apoptosis.[18] In the myocardium, galectin-3 helps translate the signal of transforming growth factor-β to increase cell cycle (cyclin D1) and direct both the proliferation of myofibroblasts and the synthesis of procollagen 1. Recombinant galectin-3 has been shown to induce cardiac fibroblast proliferation, collagen production, and cyclin D1 expression (Figure 1).[19] In aggregate, the data strongly suggest that galectin-3 is a critical participant in the pathogenesis and progression of HF.[20] Recently, galectin-3 has been shown to be pathogenic in the formation of renal fibrosis in the setting of CKD and in post-transplant models.[21] It is possible that production in one organ (heart or kidneys) could mediate disease in the other by raising circulatory levels of galectin-3, and hence mediate a chronic cardiorenal syndrome.[22]

Galectins are carbohydrate-binding proteins involved in the regulation of satellite cell signaling, immunity, and cancer.

Case 1: Galectin-3 in the General Population

A 50-year-old man is seen in the office with a concern regarding the future risks of CKD, HF, and premature death. He has no symptoms and exercises at a high level. He has a 22-year history of hypertension and, at initial evaluation, had a normal LVEF of 60%. His renal function is normal. Blood pressure has been well controlled with a variety of agents over the years and most recently he is taking benazepril, 40 mg/d. There is a family history of hypertension in first-degree relatives and a distant family history of HF death. His galectin-3 level is 16.2 ng/mL, which prompts a re-evaluation of his LVEF and blood pressure response to exercise on a treadmill examination.

In the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, galectin-3 levels were measured in 7968 individuals from the general population.[23] Normal levels of galectin-3 were found to be (in general) < 11.0 ng/mL, but increase with age and were slightly higher for women in each age category (Figure 2). In a multivariate analysis, higher levels of galectin-3 were associated with age, female sex, diabetes, hypertension, hypercholesterolemia, body mass index, and renal dysfunction

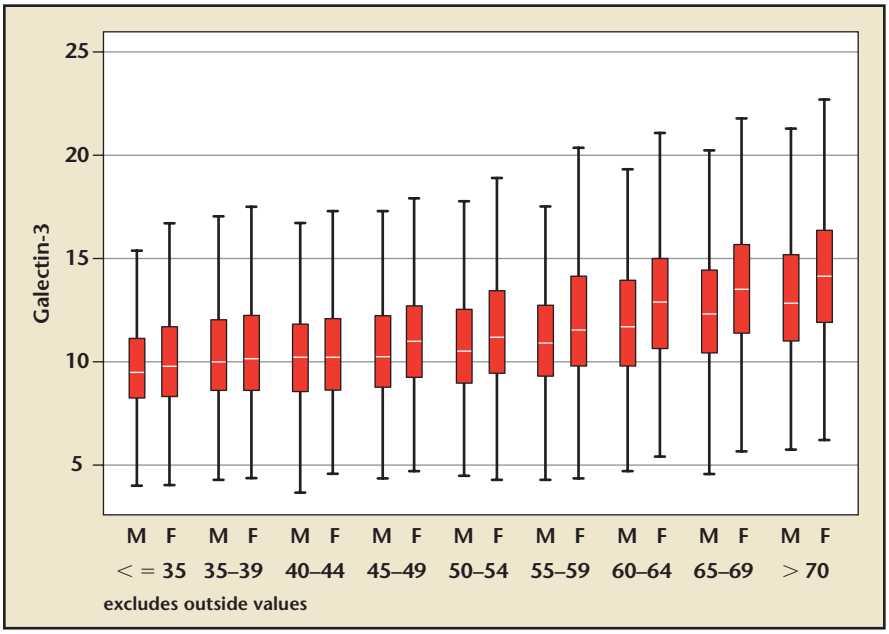


Figure 2. Measured levels of galectin-3 levels in the general population by age and sex from the Prevention of Renal and Vascular End-stage Disease (PREVEND) study. Data from de Boer RA et al.[23]

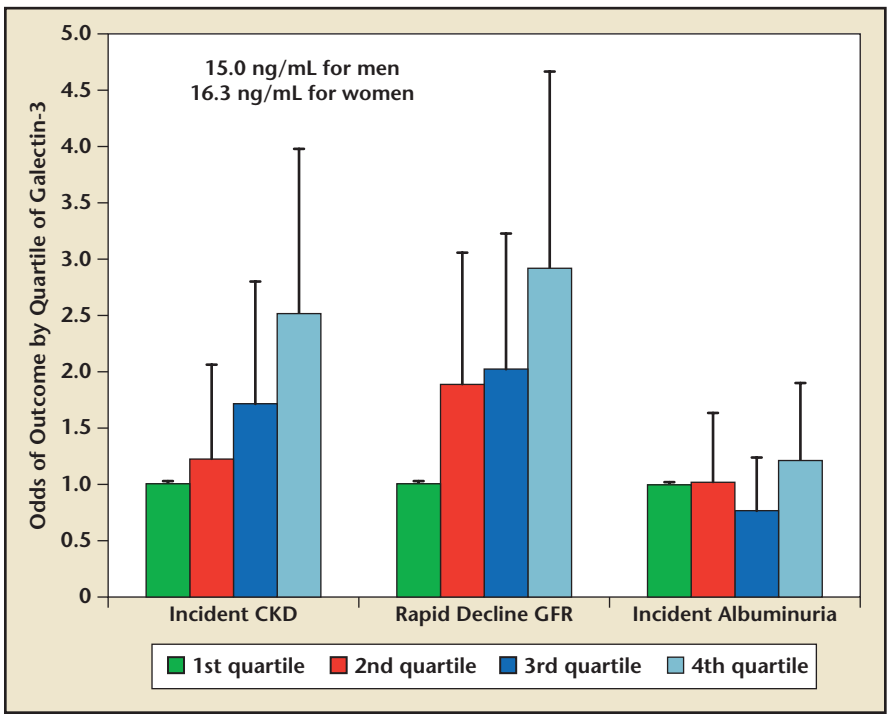
(all $P < .001$) and smoking ($P = .002$). Persons in the highest quintile of galectin-3 (median 15.6 ng/mL) incurred a 15% 10-year mortality rate compared with a 5% rate for those in the lowest quartile (median 7.7 ng/mL). Thus, population galectin-3 levels are associated with conventional cardiovascular risk factors, and as a reflection of the chronic vascular damage associated with these conditions, translate into higher all-cause mortality rates at 10 years.

This patient raises several concerns. With longstanding hypertension, the risk of the development of CKD and its rapid progression is elevated. Recent data from the Framingham Study confirmed that an elevated galectin-3 in this general population predicted the development and rapid progression of CKD (Figure 3).[24] Among Framingham participants, incident CKD developed in 277 (11.3%), and albuminuria developed in 194 (10.1%). Higher plasma levels of galectin-3 were associated with rapid decline in epidermal growth factor receptor (eGFR; $\geq$ 3 mL/min/1.73 m^2 decline) (per 1-SD log-galectin-3; adjusted odds ratio [OR] 1.49; 95% confidence interval [CI], 1.28-1.73) and a higher risk of incident CKD (eGFR $<$ 60 mL/min/1.73 m^2) (OR 1.47; 95% CI, 1.27-1.71), but not with the risk of incident albuminuria (Figure 3).

The patient's second concern is the future development of HF. Ho and colleagues,[25] in another paper from the Framingham study in which the mean age was 59 years at baseline, demonstrated that those in the highest galectin-3 tertile (15.447.7 ng/mL) had a considerably higher rate (~10% vs ~2%) of incident HF and all-cause mortality when followed over the next 11 years (Figure 4).

Thus, our patient with hypertension and an elevated galectin-3 level has higher risks of CKD with rapid progression as well as incidence HF and death. He should be considered to have stage A HF and, in addition to an angiotensin-converting enzyme inhibitor, should consider β-adrenergic blockade if tolerated from a blood pressure and exercise perspective. In addition, surveillance for CKD and HF are warranted (eg, more frequent examinations, guidelines-suggested checks on eGFR, and urine albumin:creatinine ratio, calcium, phosphorus, hemoglobin).

Figure 3. Baseline galectin-3 and risk of rapidly progressive kidney disease in the Framingham Study. CKD, chronic kidney disease; GFR, glomerular filtration rate. Adapted from van Kimmenade RR et al.[24]



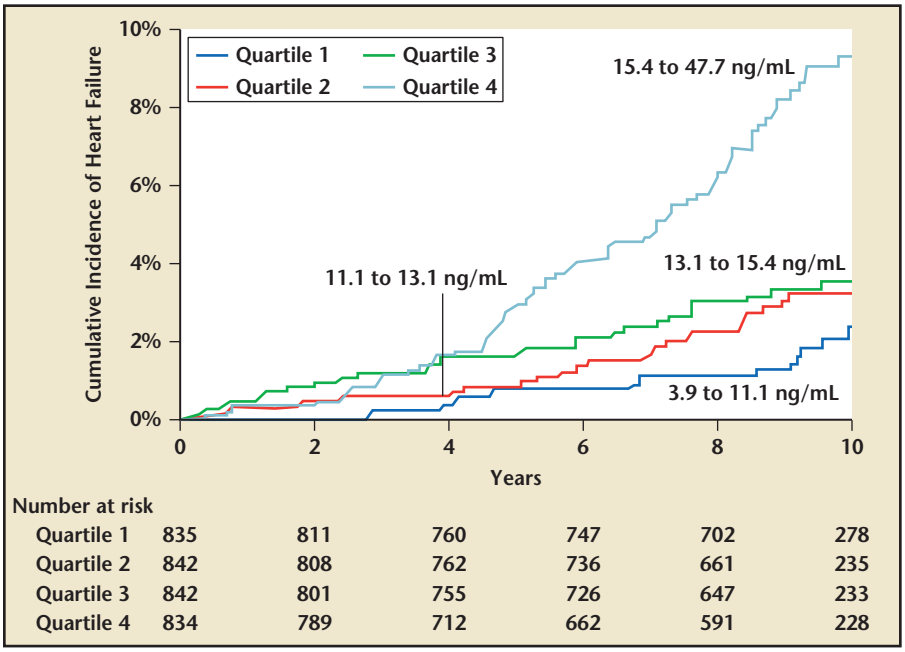


Figure 4. Rates of incident heart failure according to galectin-3 level in the Framingham Heart Study. Adapted from Ho JE et al.[25]

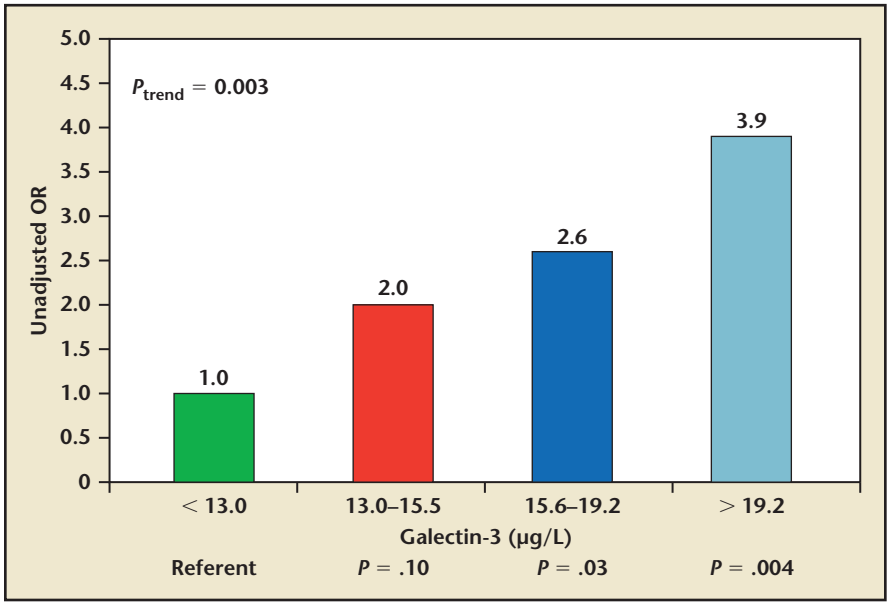
Case 2: Galectin-3 in Acute Coronary Syndrome

A 65-year-old man presents with a non–ST-segment elevation myocardial infarction. Coronary angiography reveals moderate two-vessel disease and a severe lesion in the left anterior descending artery treated with percutaneous coronary intervention (PCI) and stenting. His baseline galectin-3 is 22.1 ng/mL, brain natriuretic peptide (BNP) level is 126 pg/mL, and his LVEF after PCI is 55%. On day 3, the patient develops HF and is transferred to the intensive care unit after prompt recognition and treatment. In this case, both the galectin-3 and BNP predicted the development of cardiac failure and were clinical indicators for observation and delay of early discharge. Grandin and colleagues,[26] in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, demonstrated that a galectin-3 value > 16.7 ng/mL had an OR of 2.1 (95% CI, 1.2-3.6) for developing HF (P = .010) (Figure 5). Thus, in addition to assessment of the degree of coronary disease, LVEF, and BNP, galectin-3 appears to be a useful marker when measured at baseline in patients with acute coronary syndromes. Of note, it is likely the galectin-3 level reflects the circulating levels before the myocardial infarction occurred because acute ischemia does not rapidly induce production of the protein. So we interpret galectin-3 to represent baseline predisposition to LV dysfunction in the setting of superimposed ischemia and infarction.

Case 3: Establishing an Office Diagnosis of HF

A 52-year-old woman presents with progressive dyspnea (functional class 2) and peripheral edema. She has a history of obesity, type 2 diabetes and hypertension. There is no prior history of HF. Medications include oral nebivolol, 5 mg/d; oral ramipril, 5 mg/d; oral metformin, 500 mg three times daily; and subcutaneous insulin. She has normal cardiac examination results. Electrocardiogram reveals sinus rhythm with right bundle branch block. Cardiopulmonary stress test revealed a low peak oxygen consumption of 10.5 mg/mL/kg/min (normal for this age is 30 mL/min/kg) but normal spirometry. Coronary angiography demonstrated no significant coronary artery disease, and LVEF was normal at 65%. Echocardiography confirmed the LVEF and found a pseudonormal (grade II) pattern of diastolic dysfunction as shown in Figure 6. The

Figure 5. Rates of incident heart failure in patients after acute coronary syndrome in the Thrombolysis in Myocardial Infarction Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE-IT 22) trial. OR, odds ratio. Adapted from Grandin EW et al.[26]



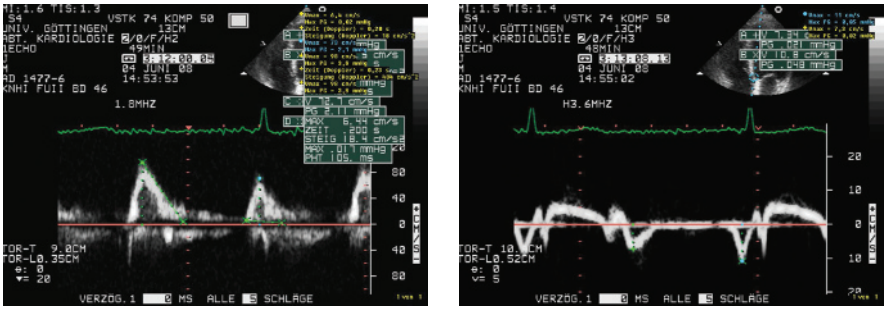


Figure 6. Office echocardiogram in a patient with exercise intolerance showing indeterminant mitral inflow and tissue Doppler for a diagnosis of diastolic dysfunction. LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVMI, left ventricular mass index; MR, mitral regurgitation; PA, pulmonary artery; TR, tricuspid regurgitation.

N-terminal pro BNP (NT-proBNP) was 230 pg/mL and galectin-3 level was elevated at 18.6 ng/mL, confirming a diagnosis of diastolic HF also referred to as HF with preserved ejection fraction (HFPEF). Oral spironolactone, 25 mg/d, was added to her regimen. This case highlights how galectin-3 is useful in the obese dyspneic patient in illuminating multiple sources of exercise intolerance and revealing significant myocardial disease.

Case 4: Galectin-3 in Established HF

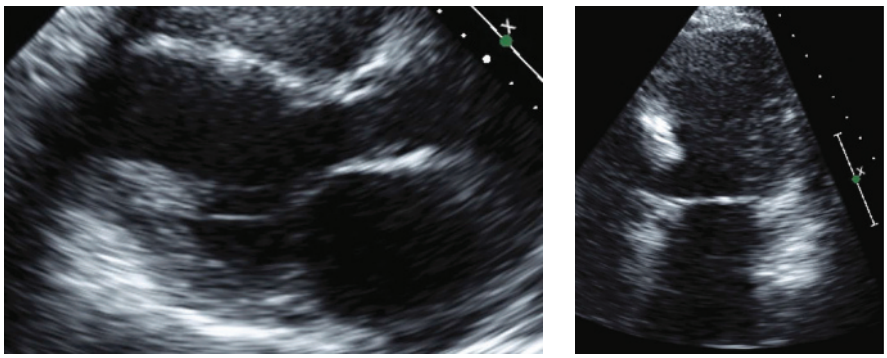
A 64-year-old woman with a history of a large anterior wall myocardial infarction 3 years ago is seen for a routine office visit; her LVEF is 30% and she has class 3 HF. Past history includes type 2 diabetes (she is not on medication), hypertension, prior atrial flutter ablation, implantable cardio defibrillator in situ, and old embolic stroke. She chronically has exercise intolerance, and S3 heart sound and 3+ edema on examination. Her echocardiogram is shown in Figure 7. Her galectin-3 level is 20.8 ng/mL. The patient is changed from quarterly to monthly visits. Oral spironolactone, 25 mg/d, is started, and her other medications remain unchanged (oral enalapril, 2.5 twice daily; oral carvedilol, 12.5 twice daily; oral bumetanide, 2 mg/d; oral amiodarone, 200 mg/d; warfarin adjusted dose; oral aspirin, 81 mg/d). Cardiac and vascular fibrosis can lead to the progression of HF by creating tissue heterogeneity and stiffness resulting in arrhythmias and sudden death or pump failure, as shown in Figure 8.

Approximately half of all HF patients will have a galectin-3 level above the upper limit of normal of 17.7 ng/mL.[23] Lin and colleagues[27] measured blood galectin-3 levels in 106 patients with stable HF with a mean age of 61 years, LVEF of 35%, and functional class of 2.2. Log galectin-3 was significantly correlated with log serum type 3 amino terminal propeptide of procollagen ($P = .006$), log tissue inhibitor of metalloproteinase-1 ($P = .025$), log metalloproteinase-2 ($P = .016$), and functional class ($P = .034$), but not age, sex, or LVEF. After multivariable adjustment, the relationship between galectin-3 and extracellular matrix turnover biomarkers remained significant, suggesting it is actively involved in extracellular matrix turnover and fibrosis.

Over 90% of patients with HF have a death that is either attributable to pump failure or arrhythmias.[8] Along the progression to death, most HF cases are characterized by frequent hospitalizations and complications from other illnesses such as renal failure and pneumonia. Thus, tools that aid in the prognosis of HF are inherently management tools as physicians deal with patients and their families in the circumstances nearing the end of life. Because progressive cardiac fibrosis is believed to be a central aspect in the progression of both systolic and diastolic dysfunction as well as the primary substrate for lethal arrhythmias, it is intuitive that a blood marker of cardiac fibrosis would be independently associated with HF hospitalization and death. In the Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study, among those patients acutely short of breath in the emergency department, log galectin-3 had

Approximately half of all HF patients will have a galectin-3 level above the upper limit of normal of 17.7 ng/mL.

Figure 7. Echocardiographic findings in a patient with ischemic cardiomyopathy and systolic dysfunction. LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVMI, left ventricular mass index; MR, mitral regurgitation; PA, pulmonary artery; TR, tricuspid regurgitation.



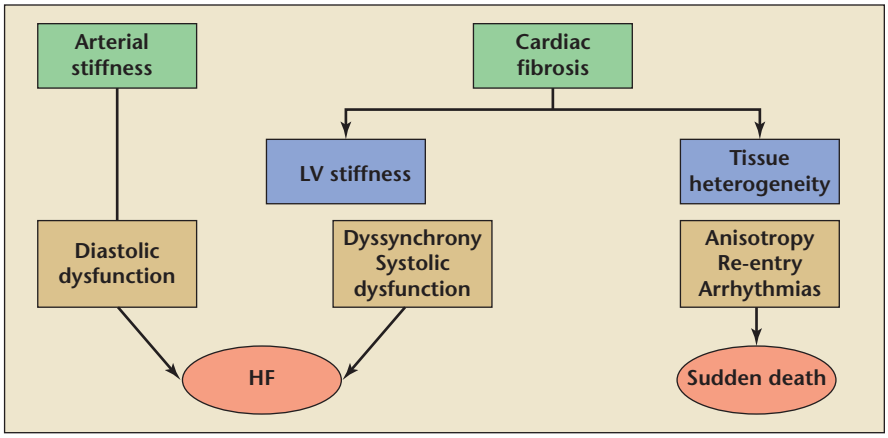


Figure 8. Cardiac fibrosis results in myocardial tissue heterogeneity and vascular stiffness. These processes predispose to arrhythmias and pump failure as the two major manifestations of HF progression. HF, heart failure; LV, left ventricular. Reproduced with permission from McCullough PA et al.[12]

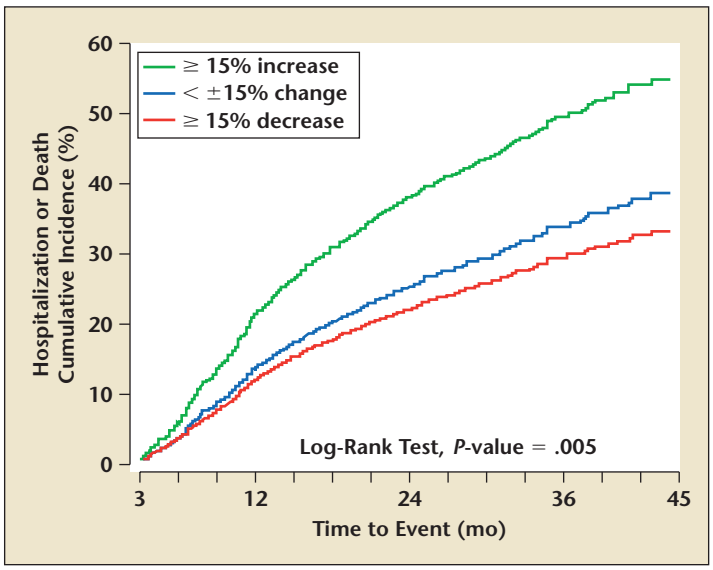
an OR of 10.3 ($P = .007$) and 14.3 ($P < .001$) for death and the combination of death or hospitalization, respectively.[24]

Case 5: Newly Diagnosed HF With Serial Measurement

A 55-year-old woman with a 9-year history of paroxysmal atrial fibrillation and HF when elevated heart rates last for several hours is seen in consultation. Past history includes three prior atrial fibrillation ablation attempts; her LVEF ranged from 35% to 50% on prior reports when atrial fibrillation lasted more than several hours. She had no significant coronary disease or diabetes, and had normal renal function. Her initial examination in the office revealed a diffuse point of maximal impulse and soft heart tones, but no S3 or other findings. Cardiac magnetic resonance imaging revealed a noncompaction cardiomyopathy, LVEF of 49%, and minimal fibrosis in the posterior left atrium. Her galectin-3 levels rose from a baseline of 14.9 to 27.9 ng/mL over the course of 9 months. The patient's subsequent disease course became complicated and she was admitted to the hospital several times with acutely decompensated HF and hyponatremia. In her case, dynamic changes in galectin-3 were congruent with the clinical course and in some instances anticipated the next clinical change with a > 15% increase indicative of progressive worsening, as shown in Figure 9.

de Boer and coworkers assessed galectin-3 in 592 subjects in the Counseling in Heart Failure (COACH) trial.[28] Levels of galectin-3 were measured prior to discharge from the hospital and then again at 6 months in the office. A doubling of galectin-3 from baseline was an independent predictor of HF rehospitalization and death after adjustment for age, sex, natriuretic peptide levels, and other adjusted hazard ratios of 3.34 (95% CI, 2.23-5.01; $P < 0.001$, baseline fourth quartile) and 1.77 (95% CI, 1.42-2.20; $P < .001$ doubling from baseline), respectively. In a recent analysis from the COACH and Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) trials in the same paper, van der Velde et al demonstrated that as little as a 15% change in outpatients can predict a poorer (increase) or more favorable (decrease) prognosis (Figure 9).[29] Thus, the relative change in galectin-3, indicating a differential in survival, is much smaller (± 15%) than with BNP or NT-proBNP where, in general, a doubling of the baseline value is the lower bound of a meaningful upward change and a 50% decrease from baseline is the lower bound of a downward change when measured over time.[30] In COACH, galectin-3 was a prognostic aid in both systolic and nonsystolic HF. In the first quartile of subjects there were more rehospitalizations than deaths, which progressed in a graded fashion to the fourth quartile, where the deaths exceeded the hospitalization events over the next 1.5 years (Figure 10).[28]

Figure 9. Relative changes in serial galectin-3 and outcomes in the Counseling in Heart Failure (COACH) and Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) trials. Reproduced with permission from van der Velde AR et al.[29]



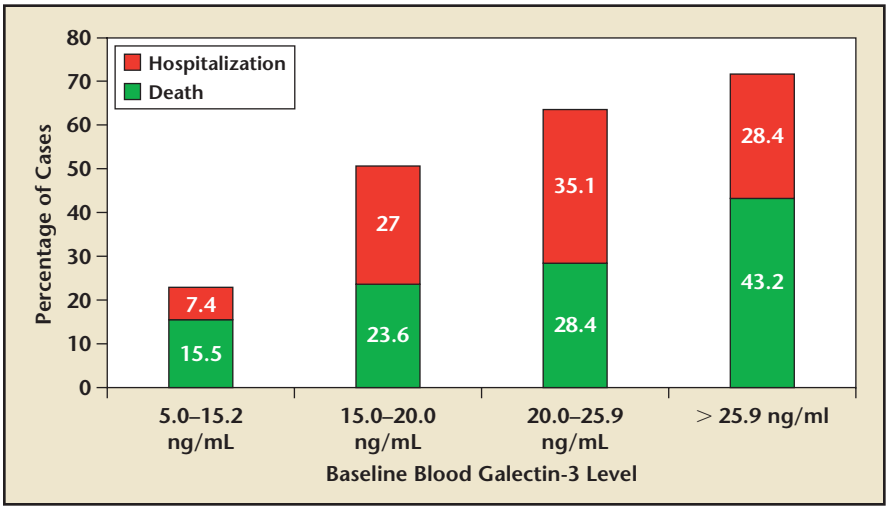


Figure 10. Rates of rehospitalization and death according to baseline galectin-3 levels in the Counseling in Heart Failure (COACH) trial. This figure demonstrates the issue of competing mortality; when the galectin-3 level is very high, death is expected before another hospitalization in many cases. Adapted from de Boer et al.[28]

Case 6: Predictive Role of Galectin-3 in Nonsystolic HF

A 63-year-old man with a 10-year history of atrial fibrillation, obesity, and class 3 dyspnea is seen for a routine visit. His past history includes type 2 diabetes (he is on oral medication), hypertension, obesity, gastric bypass surgery 8 years ago with a 100-lb weight loss (although he remains obese), and no history of coronary artery disease. On examination he has an irregularly irregular rhythm, diffuse point of maximal impulse, 2/6 murmur consistent with mitral regurgitation, and 1+ edema. The echocardiogram reveals an LVEF of 60% and moderate mitral and tricuspid regurgitation (Figure 11). His galectin-3 level is 25.1 ng/mL, which confirms a progressive fibrotic cardiomyopathy with preserved systolic function. His follow-up is advanced to 1 month instead of 6 months. The following medication changes were made: spironolactone, 25 mg/d, increased to twice daily; lisinopril, 5 mg/d, increased to twice daily; carvedilol, 12.5 mg twice daily; oral furosemide, 40 mg/d; and warfarin remained unchanged.

In this case, the predictive power of plasma galectin-3 is strong in HF patients with preserved LVEF. Nonsystolic HF (also known as diastolic HF or HF with preserved LV systolic function) is difficult to recognize among other causes of chronic dyspnea. Currently, nonsystolic HF is challenging to diagnose by echocardiography or other imaging studies and the set of associated comorbidities that define these patients (advanced age, obesity, diabetes, lung disease, CKD).[31] In this case, the mitral Doppler inflow was of limited utility in making the diagnosis of HFPEF because the patient was in atrial fibrillation and there was no a-wave. In these cases, activation of the renin-angiotensin system is believed to play a role in pathogenesis. It is has been shown that angiotensin II directly and via stimulation of aldosterone is a key neurohormone involved in the pathogenesis of cardiac fibrosis and impaired myocardial relaxation.[32] Galectin-3 levels were significantly elevated in a cohort of patients with HFPEF when compared with control subjects (18 ± 1 ng/mL vs 14 ± 1 ng/mL).[33] Thus, galectin-3, in addition to clinical and echocardiographic findings, can be used to confirm the presence of impaired diastolic function and HF.

The prognostic utility of galectin-3 yields more benefit in patients with nonsystolic HF than in those with systolic HF. In 592 hospitalized HF patients from the COACH trial, measurement of galectin-3 levels over an 18-month period provided stronger predictive power for poor outcomes in patients with

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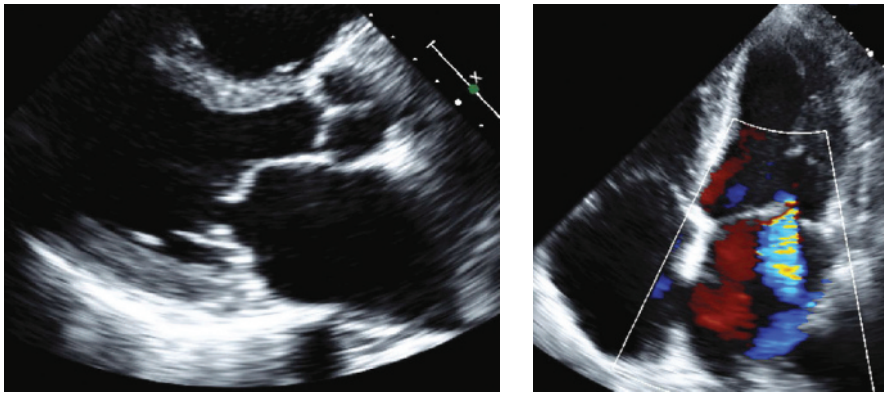
Figure 11. Echocardiographic findings in a patient with dyspnea and heart failure with preserved ejection fraction.



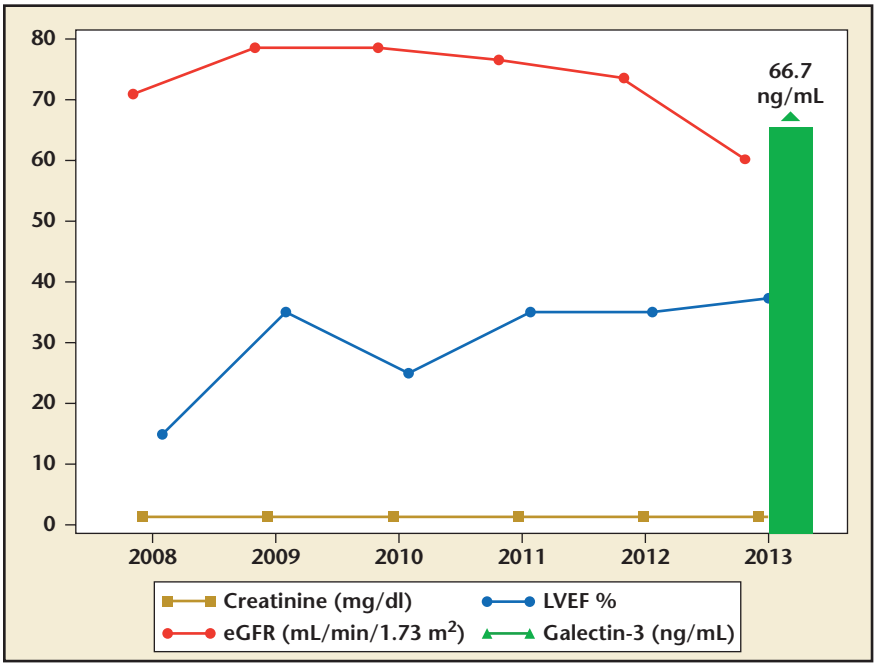


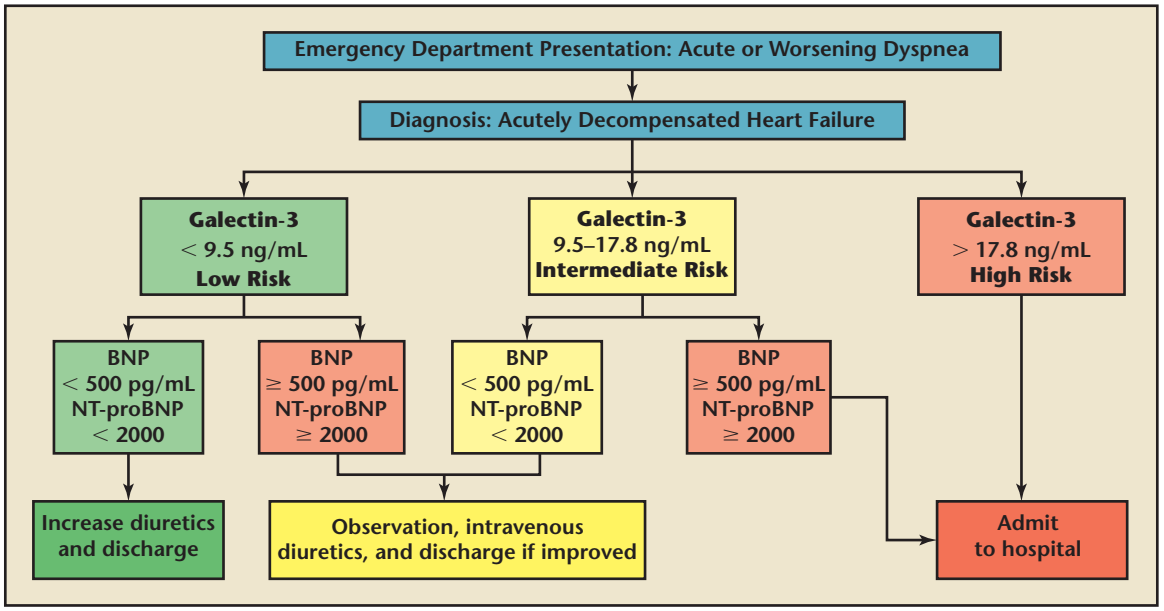
Figure 12. Serum creatinine, epidermal growth factor receptor (eGFR), and galectin-3 in a patient with combined chronic kidney disease and cardiomyopathy. LVEF, left ventricular ejection fraction.

nonsystolic HF than those with reduced LVEF.[28] In a PRIDE substudy, galectin-3 levels exhibited higher degrees of correlation with Doppler indices of diastolic function (higher E/Ea ratio, lower Ea velocity) than any other echocardiographic variable, including LVEF.[34]

Case 7: Disease Management

A 32-year-old African American man with dilated hypertensive cardiomyopathy, systolic dysfunction, superimposed diastolic HF, diabetes, diabetic nephropathy, and obesity is seen regularly in a HF management clinic for 5 years. He has class 2 symptoms on most visits. Medications include oral carvedilol, 50 mg twice daily; oral lisinopril, 20 mg/d; oral furosemide, 20 mg/d; oral spironolactone, 50 mg/d; oral hydralazine, 50 mg three times daily; oral isosorbide, dinitrate, 20 mg three times daily; glargine insulin, 22 units/d; and short-acting insulin, sliding scale 75 units/d maximum. He has had variable glycemic control over time although his blood pressure has been consistently < 130/80 mm Hg. Serial LVEF by echocardiography, eGFR, serum creatinine, and the office galectin-3 are plotted in Figure 12. In this case, the very high galectin-3 is best associated with the cardiomyopathy combined with progressive diabetic nephropathy. His high risk of death with HF based on the galectin-3 value prompted consideration for an implantable cardio defibrillator. In the Framingham study, baseline galectin-3 was predictive of progressive decline in renal filtration function but not the development of proteinuria.[35] Thus, this patient has

Figure 13. Evidence-based algorithm for the measurement of galectin-3 in patients with acutely decompensated heart failure in the emergency room. BNP, brain natriuretic peptide; NT-pro-BNP, N-terminal pro BNP.



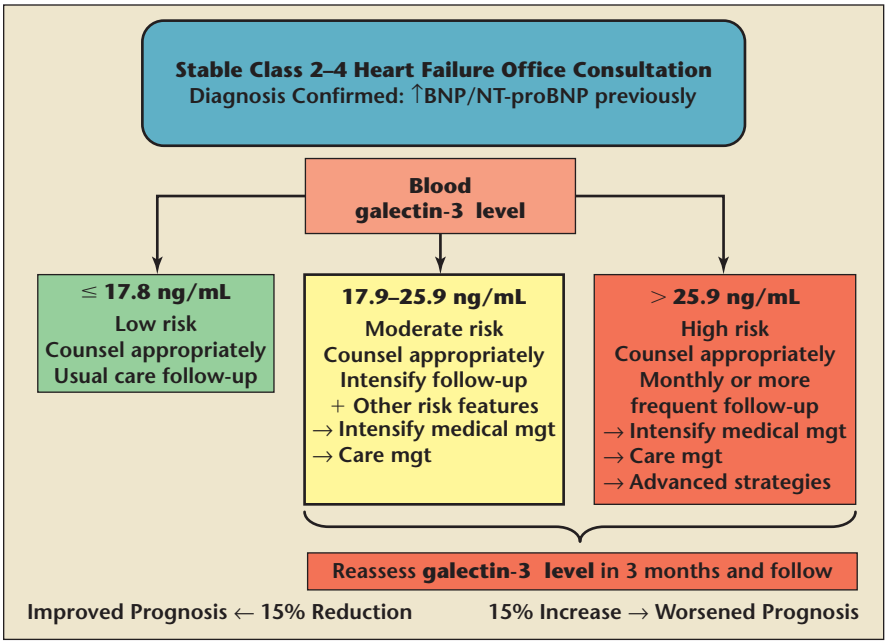


Figure 14. Evidence-based algorithm for the measurement of galectin-3 in patients after hospitalization or in the office with established heart failure. BNP, brain natriuretic peptide; Mgt, management; NT-pro-BNP, N-terminal pro BNP. Adapted from McCullough PA et al.[12]

two independent laboratory predictors of rapidly progressive CKD manifested by a decline in estimated GFR, the albumin:creatinine ratio, and galectin-3.

Integration of Galectin-3 in HF Management

A suggested approach to acutely decompensated HF is shown in Figure 13, where galectin-3 is measured in the emergency department. When galectin-3 levels are ostensibly in the normal range (< 9.5 ng/mL) and the BNP is < 500 pg/mL and NT-proBNP is < 2000 pg/mL, the patient has volume overload without active myocardial fibrosis and can potentially undergo outpatient diuresis and follow-up. Conversely, a high galectin-3 level > 17.8 ng/mL indicates that the patient is at high risk for death and rehospitalization, and therefore should be admitted for inpatient treatment. McCullough and colleagues[12] have published a proposed algorithm for recently hospitalized and ambulatory patients, as shown in Figure 14; for established HF patients with galectin-3 levels in the ≤ 17.8 ng/mL range, continuation of usual care is suggested with periodic outpatient follow-up visits. For those with galectin-3 levels in the 17.9 to 25.9 ng/mL range, more intensified care management is prompted, given an increased risk of hospitalizations and death with possibly more frequent visits, medication monitoring and adjustment, and added resources considered. In HF patients with galectin-3 levels > 25.9 ng/mL, there is an elevated risk of HF hospitalization and an even greater chance of death. In this group, the most intensive management should be considered, including HF care providers, home visits, and possibly referral for transplantation. Optimization of medical and device therapy is driven by clinical parameters such as functional class, congestion, edema, LVEF, and QRS duration.[36] However, those with a galectin-3 level > 25.9 ng/mL face a 28% chance of hospitalization and a 43% risk of death over 18 months; accordingly, they should receive particular attention for optimal care and counseling, in appropriate situations, for end-of-life care.

Conclusions

Galectin-3 induces cardiac fibroblast proliferation, collagen deposition, and ventricular dysfunction, and is the first commercially available assay measuring a pathogenic factor in HF. In the general population, elevations of galectin-3 above the normal range are predictive of both progressive CKD and the development of HF and death. In patients with multifactorial dyspnea and preserved LVEF, galectin-3 may help establish or rule out a diagnosis of HF. In those with chronic HF and galectin-3 levels > 25.9 pg/mL or a doubling of galectin-3 from any level, high rates of hospitalization and death can be expected. Our case summaries and review indicate galectin-3 is a valuable tool in both primary care and cardiovascular medicine for risk detection, diagnosis, prognosis, and management of patients at risk for or with established HF. ■

In HF patients with galectin-3 levels > 25.9 ng/mL, there is an elevated risk of HF hospitalization and an even greater chance of death. In this group, the most intensive management should be considered, including HF care providers, home visits, and possibly referral for transplantation.

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MAIN POINTS

- In the failing human heart, considerable quantities of myocardium can be replaced with collagen and interstitial matrix proteins, leading to the clinical observations of both diastolic and systolic dysfunction. Chronic kidney disease (CKD) is commonly associated with heart failure (HF), with the most common determinants being longstanding hypertension and type 2 diabetes.
- Galectin-3 is an approximately 30 kDa glycoprotein that has a carbohydrate-recognition-binding domain of approximately 130 amino acids that enable the binding of β-galactosides. It is encoded by a single gene, *LGALS3*, located on chromosome 14, locus q21–q22, expressed in the nucleus and mitochondria.
- It has been recently appreciated that, similar to replacement fibrosis in the myocardium, loss of renal parenchyma and nephron units is supplanted by fibrosis, which is directed by macrophages secreting galectin-3. Data strongly suggest that galectin-3 is a critical participant in the pathogenesis and progression of HF.
- Galectin-3 induces cardiac fibroblast proliferation, collagen deposition, and ventricular dysfunction, and is the first commercially available assay measuring a pathogenic factor in HF. In the general population, elevations of galectin-3 above the normal range are predictive of both progressive CKD and the development of HF and death.