Clinical Investigation

Prognostic Value of Galectin-3 for Adverse Outcomes in Chronic Heart Failure

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ABSTRACT

Background: Clinical studies have suggested the prognostic value of galectin-3, a marker of fibrosis, in chronic heart failure. However, the specific role of galectin-3, compared with established biomarkers, remains uncertain.

Methods and Results: The Penn Heart Failure Study was an ambulatory heart failure cohort that included 1385 participants with reduced (1141), preserved (106), and recovered (138) left ventricular ejection fraction (LVEF). Cox regression models determined the association between galectin-3 and risk of all-cause mortality, cardiac transplantation, or placement of a ventricular assist device. Receiver operating characteristic curves compared the prognostic accuracy of galectin-3, high-sensitivity soluble Toll-like receptor 2 (ST2), troponin I, and B-type natriuretic peptide (BNP) at 1 and 5 years. Higher galectin-3 levels were associated with an increased risk of adverse events (adjusted hazard ratio of 1.96 for each doubling in galectin-3; $P < .001$). This association was most pronounced among participants with preserved LVEF (adjusted hazard ratio 3.30; $P < .001$). At 5 years, galectin-3 was the most accurate discriminator of risk among participants with preserved LVEF (area under the curve 0.782; $P = .81$ vs high-sensitivity ST2; $P = .029$ vs troponin I; $P = .35$ vs BNP). BNP was most accurate among participants with reduced and recovered LVEF (areas under the curves 0.716 and 0.728, respectively).

Conclusions: Galectin-3 could have prognostic value for long-term events among patients with heart failure and preserved ejection fraction. (*J Cardiac Fail 2016;22:256–262*)

Key Words: Biomarker, ejection fraction, risk stratification, ventricular function.

Chronic heart failure imparts a major health burden and financial cost to an aging population.[1,2] Clinical research in heart failure has had a major focus on biomarkers to quantify the complex biologic processes implicated in the pathogenesis of the cardiomyopathy and the ability of those biomarkers to stratify heart failure patients regarding their risk of adverse outcomes. Accurate risk stratification can guide the clinical management of heart failure patients and enable clinicians to identify high-risk patients that might require initiation of advanced therapies. Established biomarkers of heart failure include troponin, a marker of myocyte injury, and B-type natriuretic peptide (BNP), a marker of neurohormonal activation; these biomarkers are widely used in the clinical care and management of heart failure patients.[3,4] Newer biomarkers include high-sensitivity soluble Toll-like receptor 2 (ST2), a marker of myocyte stress.[5]

Recently, galectin-3 has emerged as a biomarker of inflammation and fibrosis in heart failure. Galectin-3 is a soluble

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See page 261 for disclosure information.

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β-galactoside–binding lectin released by activated cardiac macrophages that binds to and activates fibroblasts, forming collagen and resulting in fibrosis.[6–8] Tissue fibrosis is a central pathway in the progression of heart failure. Cardiac fibrosis impairs ventricular function and contributes to both systolic and diastolic dysfunction. Animal studies have shown that galectin-3 plays a key role in tissue fibrosis and ventricular remodeling.[8–10] In particular, galectin-3 is expressed at higher levels in cardiac fibroblasts.[11] Human studies have demonstrated the prognostic utility of galectin-3 in heart failure.[12] Several cohort studies have exhibited the ability of galectin-3 to predict major events in heart failure, such as death and hospitalization.[13–15]

Results have been inconsistent regarding the relative prognostic utility of galectin-3 compared with established markers (particularly BNP and ST2).[12] Although several studies have shown that galectin-3 is independently associated with outcomes after adjustment for BNP, others have shown that galectin-3 does not improve prognostic accuracy when combined with BNP.[16–20] In addition, only 1 small study with limited follow-up compared the prognostic value of galectin-3 between patients with reduced and preserved left ventricular ejection fraction (LVEF).[21] Therefore, it is unknown how the prognostic utility of galectin-3 compares with established biomarkers, as well as whether the prognostic value of galectin-3 differs among heart failure patients with reduced, preserved, or recovered ejection fraction.

We therefore sought to characterize the independent determinants of galectin-3 levels, determine the association of galectin-3 levels with the risk of major adverse events in heart failure, and compare the ability of galectin-3 to predict major adverse events with that of established biomarkers (high-sensitivity ST2, troponin I, and BNP). Our primary analysis focused on a large cohort of ambulatory heart failure patients with a broad spectrum of disease. Secondary analyses focused on patient subgroups with different "phenotypes" of heart failure defined by their LVEF and subgroups with different cardiomyopathy etiologies.

Materials and Methods

Study Population

The Penn Heart Failure Study, sponsored by the National Heart, Lung, and Blood Institute, was a prospective cohort study of outpatients with chronic heart failure recruited from referral centers at the University of Pennsylvania (Philadelphia, Pennsylvania), Case Western Reserve University (Cleveland, Ohio), and the University of Wisconsin (Madison, Wisconsin). The primary inclusion criterion was a clinical diagnosis of heart failure as determined by a heart failure specialist. Participants were excluded if they had a noncardiac condition resulting in an expected mortality of <6 months as judged by the treating physician or if they were unable to provide informed consent. The resulting cohort spanned a full spectrum of heart failure severity, ranging from mild disease to severe disease requiring advanced therapies. Every participant provided written informed consent. Participating Institutional Review Boards approved the study protocol.

Data Collection

At the time of study entry, detailed clinical data were obtained with the use of standardized questionnaires administered to the participant and physician, with verification through medical records. Subsequent adverse events—all-cause mortality, cardiac transplantation, and placement of a ventricular assist device (VAD)—were ascertained every 6 months by means of direct contact with participants and verified through death certificates, medical records, or family members. Outcomes were collected through September 2013. Participants with a VAD placement before study entry were excluded from the analysis. We previously classified participants into 3 "phenotypes" of heart failure based on LVEF: reduced, preserved, and recovered LVEF.[22] Participants were classified as "reduced" if echocardiography at study entry showed an LVEF <50%. Participants with normal left ventricular function as defined by an LVEF ≥50%, were further classified as either "preserved" or "recovered" based on retrospective chart review of earlier echocardiograms. Participants who had previously documented LVEF of only ≥50% were classified as "preserved;" those who had a documented history of LVEF <50% were classified as "recovered."

Biomarker Assays

Biomarker measurement was performed for participants recruited from October 2003 to May 2009. Blood samples were obtained at the time of study entry, processed, and stored at −80°C until the time of assay. Galectin-3 chemiluminescent microparticle immunoassays were performed on the Architect i2000SR instrument (Abbott Laboratories, Wiesbaden, Germany).[23] The total coefficient of variation was <8%. The limit of detection was ≤1.7 ng/mL; the linear measurement range was 5.5–103.1 ng/mL. BNP, troponin I, and creatinine were measured with the use of standard Architect immunoassays (Abbott Laboratories, Abbott Park, Illinois). High-sensitivity ST2 was measured with the use of a sandwich monoclonal immunoassay (Presage ST2 Assay; Critical Diagnostics, San Diego, California). The satisfactory performance of these assays was previously described.[24] Biomarker values lower than the limit of detection were replaced with the lower limit (eg, 0.005 ng/mL for troponin I).

Statistical Methods

Standard descriptive statistics were used to summarize participant characteristics at study entry. Independent determinants of galectin-3 levels (log transformed) were ascertained from a multivariable linear regression model. Candidate variables were: age, sex, race (white, black, other), cardiomyopathy etiology (ischemic, nonischemic), New York Heart Association (NYHA) functional classification, LVEF, heart failure phenotype (reduced, preserved, recovered LVEF), cardiac resynchronization therapy, defibrillator use, body mass index, and creatinine. For continuous variables (eg, age), linearity was evaluated with the use of scatterplot smoothers. The inclusion of variables was based on a stepwise model-selection procedure to choose the subset of variables that minimized the Akaike information criterion.

Cox regression models were used to estimate the association between galectin-3 and risk of the composite outcome of all-cause death, cardiac transplantation, or VAD placement. Participants who were alive and free of cardiac transplantation or VAD placement at the end of follow-up were censored. Galectin-3 was transformed with the use of a log (base 2) transformation such that the hazard ratio compared 2 populations whose galectin-3 level differed by a