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Galectin-3 Levels and Outcomes after Myocardial Infarction: A Community Study

Rabea Asleh, MD, PhD, MHA[a], **Maurice Enriquez-Sarano, MD**[a], **Allan S. Jaffe, MD**[a], **Sheila M. Manemann, MPH**[b], **Susan A. Weston, MS**[b], **Ruoxiang Jiang, BS**[b], and **Véronique L. Roger, MD, MPH**[a,b]

[a]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota

[b]Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota

Abstract

BACKGROUND: Galectin-3 (Gal-3) is implicated in cardiac fibrosis but its association with adverse outcomes after myocardial infarction (MI) is unknown.

OBJECTIVES: To examine the prognostic value of Gal-3 in a community cohort of incident MI.

METHODS: A population-based incidence MI cohort was prospectively assembled in Olmsted County, MN, between 2002 and 2012. Gal-3 levels were measured at the time of MI. Patients were followed for heart failure (HF) and death.

RESULTS: We enrolled 1342 patients (mean age 67.1 years, 61.3% male, 78.8% non-ST-elevation MI). Patients with elevated Gal-3 were older and had more comorbidities. Over a mean follow-up of 5.4 years, 484 patients (36.1%) died and 368 (27.4%) developed HF. After adjustment for age, sex, comorbidities and troponin, patients with Gal-3 values in tertiles 2 and 3 had a 1.3-fold (95% CI, 0.9–1.7) and a 2.4-fold (95% CI, 1.8–3.2) increased risk of death, respectively (P_{trend}<0.001) compared with patients with Gal-3 values in tertile 1. Patients with Gal-3 values in tertiles 2 and 3 had a higher risk of HF with hazard ratios of 1.4 (95% CI, 1.0–2.0) and 2.3 (95% CI, 1.6–3.2), respectively (P_{trend}<0.001). With further adjustment for soluble suppression of tumorigenicity-2 (sST2), elevated Gal-3 remained associated with increased risk of death and HF. The increased risk of HF did not differ by HF type and was independent of the occurrence of recurrent MI.

CONCLUSIONS: Gal-3 is an independent predictor of mortality and HF post MI. These findings suggest a role for measuring Gal-3 levels for risk stratification post MI.

CONDENSED ABSTRACT

The present study evaluates the prognostic value of galectin-3 (Gal-3) measured at the time of incident myocardial infarction (MI) in a large contemporary community cohort. This is the first

Address for correspondence: Véronique L. Roger MD, MPH. Department of Cardiovascular Diseases and Department of Health Sciences Research, Mayo Clinic. 200 First Street SW, Rochester, MN 55905, USA. Fax: 507-284-1516; Telephone: 507-538-6916; veronique.roger@mayo.edu.

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population-based study to examine the association between Gal-3 levels and long-term outcomes after MI demonstrating that Gal-3 is a strong predictor of mortality and heart failure post MI independently of other known prognostic factors and biomarkers, including troponin and soluble suppression of tumoriegenicity-2 (sST2). These findings support the use of Gal-3 as a biomarker for risk stratification in patients with MI.

Keywords

Myocardial infarction; Galectin-3; Biomarkers; Heart failure; Mortality; Population-based study

INTRODUCTION

Over the last two decades, population-based studies have demonstrated major changes in the epidemiology of myocardial infarction (MI). Patients with MI now present at older ages, without ST elevation, and more frequently survive the acute phase (1–3). Even after rapid restoration of coronary blood flow by acute intervention, the risk of adverse outcomes including heart failure (HF) and death remains substantial although its presentation is also evolving (4). Indeed, when HF occurs, ejection fraction (EF) is more often preserved which may reflect evolving mechanisms of the left ventricular (LV) remodeling process leading to progressive dysfunction (5). Thus, it is important, given the changing epidemiology of MI, to evaluate risk stratification in the current population of patients with MI and to investigate whether novel biomarkers, and in particular those implicated in cardiac fibrosis and remodeling, add prognostic information over clinical information.

We recently reported on risk stratification approaches among a prospective contemporary cohort of patients with MI in the community. We reported that the performance of scores historically recommended for MI risk stratification was disappointing in contemporary community cohorts (6), underscoring the need to revisit these approaches. We examined the contribution of a novel biomarker of fibrosis, soluble suppression of tumorigenicity 2 (sST2), and found that sST2 was frequently elevated in MI and that higher values were associated with a large excess risk of death and HF independently of troponin (7). These data underscored the importance of studying risk stratification in contemporary cohorts of optimal clinical relevance and the prognostic value of markers of fibrosis, such as sST2. Galectin-3 (Gal-3), a β-galactoside-binding lectin mainly secreted by activated macrophages, is also reflective of fibrosis and cardiac remodeling in response to myocardial injury (8–10). While biologically plausible, the hypothesis of an association between Gal-3 and post MI outcomes remains unproven as small reports in convenience samples of Gal-3 in acute coronary syndrome (ACS) yielded conflicting results (11–13). Further, a comparison of Gal-3 and sST2 using rigorous risk prediction statistical methods is lacking after MI. To address this gap in knowledge, we used robust and complementary methods including calibration, discrimination, and reclassification analyses to investigate the association between Gal-3 and outcomes after MI, and its incremental value over troponin and sST2. We studied a large geographically defined contemporary cohort of prospectively enrolled incident (first ever) MI to avoid contamination of the results by preexisting myocardial injury and scarring.

METHODS

Study Design and Setting

This prospective study was conducted in Olmsted County, Minnesota (2017 population of approximately 154,930) utilizing the resources of the Rochester Epidemiology Project (REP) (14,15), which is a medical records linkage system allowing virtually complete capture of health care utilization and outcomes of nearly all persons living in the county. Complete recording of clinical events in Olmsted County is possible because of its relative isolation from other urban centers, thus enabling the delivery of most health care to local residents by few health care facilities, including Mayo Clinic, Olmsted Medical Center, and their affiliated hospitals. All medical diagnoses are maintained through an electronic index, and patients can be identified through their in- and outpatient contacts across the local medical providers (15). The demographic and ethnic characteristics of Olmsted County residents are representative of the state of Minnesota and the Midwest region of the United States with similar broad disease trends and age- and sex-specific mortality rates to that observed in national data (15). This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Identification and Validation of the Myocardial Infarction Cohort

Olmsted County residents admitted to Mayo Clinic hospitals from November 1, 2002, through December 31, 2012, with a cardiac troponin T level of 0.03 ng/ml or higher were identified within 12 hours of the blood draw. Written consent was obtained from all participants or next of kin and samples stored for future use. MI cases were validated using standard epidemiologic algorithms integrating cardiac pain, electrocardiogram (ECG) changes, and elevated troponin T as previously described (1,16) and following current guidelines (17); only incident (first-ever) MI cases were included in this study. A significant change (increase or decrease) in troponin levels was considered when the difference between successive troponin measurements was 0.03 ng/ml or higher to ensure that this is greater than the level of imprecision of the assay at all concentrations (17). All cases were reviewed to ensure there were no alternative causes resulting in biomarker elevation.

Biomarker Measurements

Cardiac troponin T was measured as part of standard care using a sandwich electrochemiluminescence immunoassay on the Elecsys 2010 in the laboratories of the Department of Medicine and pathology at Mayo Clinic.

sST2 was measured from stored plasma samples using a high-sensitivity sandwich monoclonal immunoassay (Presage® ST2 assay, Critical Diagnostics, San Diego, CA, USA). All samples were collected via peripheral vein into EDTA-containing tubes and then centrifuged immediately and stored at -70^{0}C prior to analysis at core laboratories. The antibodies used in the Presage® assay were generated from a recombinant protein based upon the human cDNA clone for the complete soluble sequence (18). This platform offers improved accuracy in quantifying sST2 levels, particularly at lower concentrations. This specific assay has high sensitivity; the reliability of running the Presage® sST2 assay on EDTA plasma samples stored at -70^{O}C (as per biomarker core lab) has been established in

numerous studies (19–21). Calibration and standardization of this assay were performed according to the manufacturer's protocol. Previous reports document the intra- and inter-assay coefficients of variation as <2.5% and <4.0%, respectively (18).

Gal-3 concentrations were measured from the stored plasma samples by enzyme-linked immunosorbent assay (ELISA; BG Medicine, Waltham, Massachusetts) on an automated plate reader with high sensitivity and reliability measures. According to the manufacturer`s protocol, the measurement values of Gal-3 using this assay can range between 1.4 and 94.8 ng/ml, and the overall intra- and inter-assay coefficients of variation (CVs) have been reported as approximately 3.4% and 8.5%, respectively.

Clinical Characteristics

CVD risk factors, comorbid conditions, MI severity indicators, and use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB) and beta blockers at hospital dismissal were collected from the medical records by trained nurse abstractors. Body mass index (BMI, kg/m^2) was calculated using the current weight and earliest adult height. Cigarette use was classified as current versus no smoker. Clinical definitions were used for hypertension, diabetes mellitus, hyperlipidemia, and prior HF. Comorbidity was assessed by the Charlson comorbidity index (22) which consists of 17 conditions weighted according to the degree to which they predict death. The presence of ST-elevation MI was determined using the Minnesota Code Modular ECG Analysis System (23). Ejection fraction was recorded based on the closest EF measurement within 30 days after the MI diagnosis date as previously described (24).

Outcome Measures

All participants were followed for HF and death through their complete inpatient and outpatient community medical records from the index MI to date of last follow-up or December 31, 2014, whichever occurred first. HF was identified using International Classification of Diseases, 9^{th} Revision (ICD-9) code 428 and validated using the Framingham criteria (25) following a previously reported approach, with minimal missing data and excellent inter-observer agreement (26). HF type was determined by echocardiographic measurements of left ventricular EF using the closest measurement to HF diagnosis (with a predefined maximum period of 90 days). HF was classified as HF with reduced EF (HFrEF) when EF<50% and HF with preserved EF (HFpEF) when EF≥50%. Death (occurrence and date) was ascertained from the medical records and death certificates obtained from the county and state by the REP. Deaths were classified as cardiovascular (CV) (ICD-9 codes 390–459, ICD-10 codes I00-I99) based on American Heart Association classifications (27).

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (25^{th}-75^{th} percentile), as appropriate; categorical variables were expressed as percentages. Baseline clinical characteristics were compared across Gal-3 tertiles using linear regression and Mantel-Haenszel chi-squared tests, as appropriate.

Differences in all-cause death after MI were assessed using the Kaplan-Meier method according to Gal-3 tertiles and compared with the log-rank test. The cumulative incidence of HF following MI was estimated according to Gal-3 tertiles, treating death as a competing risk. Cox proportional hazards regression models were constructed to examine the association between Gal-3 and outcomes (death, CV death, HF, HFpEF and HFrEF) after MI. Splines indicated a linear relationship between Gal-3 and all outcomes. Results are reported for each 10-unit increase in Gal-3 and also according to Gal-3 tertiles using the lowest tertile as the referent to aid in interpretation. Models were adjusted for age and sex with further adjustment for the Charlson comorbidity index and maximum troponin T measurement. HF prior to the MI was also adjusted for in the models predicting HF, HFpEF and HFrEF. Analyses were repeated for patients who survived at least 30 days after the incident MI. The proportional hazards assumption was tested using the scaled Schoenfeld residuals and found to be valid.

Several measures were used to assess the incremental prognostic value of Gal-3, modeled as a log-transformed continuous variable, with and without the inclusion of sST2, also log-transformed, in the reference models which included age, sex, Charlson comorbidity index, and maximum troponin T. Calibration was assessed using the likelihood ratio test, Akaike information criterion (AIC), and Bayesian information criterion (BIC). Additionally, a group-based measure of calibration was assessed using a novel method utilizing a model-based framework that provides a natural extension to survival data (28). Discrimination was assessed using the C-statistic. Reclassification was assessed within the Cox model framework using the continuous net reclassification improvement (NRI) (29,30), in addition to its two components, event and nonevent NRI, with a 5-year cutoff to determine event status. Data analyses were performed using SAS software, version 9.4 (SAS institute Inc, Cary, NC) and R version 3.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Population

Between November 1, 2002 and December 31, 2012, 1342 patients with incident MI were enrolled in the study and had stored plasma samples available for Gal-3 and sST2 measurement. The mean (SD) age of the cohort was 67.1 (14.9) years, 61.3% were male, and 78.8% presented with non-ST-elevation MI. The median (25^{th}, 75^{th} percentile) time from MI event to blood sample collection for Gal-3 and sST2 was 2 (1, 3) days. The median (25^{th}, 75^{th} percentile) Gal-3 level was 18.1 (13.3, 25.5) ng/ml; 457 (34%) had elevated Gal-3 compared to the published reference value of 22.1 ng/ml (31). The median (25^{th}, 75^{th} percentile) sST2 level was 47.0 (32.1, 99.3) ng/ml; 676 (50%) had elevated sST2, compared with published normal values from the Framingham Heart Study (32).

Patients were divided into 3 groups according to Gal-3 concentrations: tertile 1 (<15.1 ng/ml), tertile 2 (15.1–22.4 ng/ml), and tertile 3 (>22.4 ng/ml). The range of Gal-3 values in each tertile were 4.46–15.00 ng/ml in tertile 1, 15.02–22.40 ng/ml in tertile 2, and 22.404–115.0 in tertile 3. Patients with higher Gal-3 levels were older, more likely to be female, had more diabetes and hypertension, had more comorbidities than patients with lower Gal-3 levels, were more likely to present with Q waves on the ECG, anterior MI, and Killip class

>1, but were less likely to present with ST-elevation (Table 1); they were less likely to be current smokers, to have familial coronary disease, had lower EF, and were less likely to be prescribed beta blockers at discharge.

Galectin-3 and Death

During a mean (SD) follow-up of 5.4 (3.5) years, 484 (36.1%) patients died. Elevated Gal-3 was associated with increased mortality with 5-year estimates of 10.2%, 24.4%, and 51.9% for patients with values in tertile 1, 2, and 3, respectively (P<0.001) (Central Illustration A).

Elevated Gal-3 was strongly associated with death in the unadjusted model with the association remaining strong after adjustment for key clinical characteristics including age, sex, Charlson index, and maximum troponin T measurement (Table 2). From the adjusted model, the association followed a dose-response pattern with a 30% increased risk of death for each 10-unit increase in Gal-3 (HR 1.30, 95% CI 1.24–1.36) or, when analyzing tertiles of Gal-3, a 26% increased risk of death for patients with Gal-3 values in tertile 2 (HR 1.26, 95% CI 0.93–1.70) and more than a 2-fold increased risk for patients with Gal-3 values in tertile 3 (HR 2.35, 95% CI 1.76–3.15) compared to patients with Gal-3 values in tertile 1 (P_{trend}<0.001). In sensitivity analyses we examined the effect of adjusting for a number of additional variables. First, the Charlson comorbidity index was replaced with the individual comorbidities that comprise the Charlson index. This did not materially change the association between Gal-3 level and death (HR 1.34, 95% CI 1.27–1.41 for each 10-unit increase in Gal-3; P<0.001). Second, further adjustment for discharge medications (including beta blockers and ACE inhibitors/ARBs) and EF within 30 days post MI each resulted in a slight attenuation of the association between Gal-3 level and death (discharge medications: HR 1.23, 95% CI 1.16–1.30; P<0.001 and EF: HR 1.24, 95% CI 1.16–1.32; P<0.001 for each 10-unit increase in Gal-3). Finally, additional adjustment for time from MI symptom onset to Gal-3 measurement, estimated glomerular filtration rate, current smoking status, hypertension and hyperlipidemia did not change the associations (data not shown). When restricted to individuals who survived at least 30 days after the MI, the associations from the adjusted model were similar (HR 1.25, 95% CI: 1.18–1.32; P<0.001 for a 10-unit increase in Gal-3; or HR 1.25, 95% CI: 0.92–1.70 and HR 2.20, 95% CI: 1.62–2.99 for patients with Gal-3 values in tertile 2 and 3, respectively; P_{trend}<0.001).

Similarly for CV death (n=188), higher Gal-3 tertile was associated with an increased risk of CV death that followed a dose-response pattern (Table 2) and remained independent of key clinical characteristics known to predict risk after MI.

Galectin-3 and Heart Failure

During the same follow-up, 368 (27.4%) patients experienced a HF event (53 in Gal-3 tertile 1, 115 in Gal-3 tertile 2, and 200 in Gal-3 tertile 3). Higher Gal-3 tertile was significantly associated with a higher cumulative incidence of HF (Central Illustration B) treating death as a competing risk. The cumulative incidence of HF at 5-years of follow-up was 11.6%, 22.9%, and 43.8% for patients with Gal-3 values in tertiles 1, 2, and 3, respectively (P<0.001). Elevated Gal-3 levels were associated with a significant increase in HF risk (Table 2). After adjustment for age, sex, Charlson index, maximum troponin T and HF prior

to the MI, there was a 15% increased risk of HF for each 10-unit increase in Gal-3 (HR 1.15, 95% CI 1.09–1.22). When analyzing tertiles of Gal-3, a dose-response pattern was evident with a 40% increased risk of HF for patients with Gal-3 values in tertile 2 (HR 1.40, 95% CI: 1.00–1.96) and more than a 2-fold increased risk for patients with Gal-3 values in tertile 3 (HR 2.25, 95% CI: 1.61–3.15; $P_{trend}<0.001$). Further adjustment for (1) recurrent MI as a time-dependent covariate, (2), the individual comorbidities that comprise the Charlson index, and (3) time from MI symptom onset to Gal-3 measurements, estimated glomerular filtration rate, current smoking status, hypertension, hyperlipidemia, EF post MI, and discharge medications did not materially change the associations (data not shown). When restricted to individuals who survived at least 30 days after the MI, the associations from the fully adjusted model were similar (HR 1.16 (1.09– 1.24); P<0.001 for a 10-unit increase in Gal-3; HR 1.43, 95% CI: 1.02–2.00 and HR 2.18, 95% CI: 1.54–3.07 for patients with Gal-3 values in tertile 2 and 3, respectively; $P_{trend}<0.001$). Stratified by HF type, the association between Gal-3 levels and HF risk did not differ appreciably between HFrEF and HFpEF and remained significant after adjustment (Table 2).

Incremental Prognostic Value of Galectin-3

In the final stage of the analyses, log-transformed sST2 was added to the reference model to evaluate the incremental value of Gal-3 over sST2. With sST2 in the model, it is important to note that higher values of Gal-3 remained associated with higher risk of death although the HRs were attenuated (HR 1.21, 95% CI 1.16–1.27; $P<0.001$ for a 10-unit increase in Gal3; HR 1.09, 95% CI: 0.80–1.47 and HR 1.64, 95% CI 1.22–2.22 for patients with Gal-3 values in tertile 2 and 3, respectively; $P_{trend}<0.001$). When examining HF as the outcome, the association between higher Gal-3 and increased risk of HF remained when sST2 was added to the reference model (HR 1.08, 95% CI 1.02–1.15; $P=0.009$ for a 10-unit increase in Gal3; HR 1.24, 95% CI 0.89–1.74 and HR 1.72, 95% CI 1.22–2.43 for patients with Gal-3 values in tertile 2 and 3, respectively; $P_{trend}=0.001$).

For both outcomes (death and HF), the likelihood ratio test indicated improved model fit when Gal-3 and sST2, both log-transformed, were each added to the reference model and when Gal-3 was added to the model that included sST2 (Table 3). The AIC and BIC were lower in the models that included Gal-3 and sST2 as compared to the reference model, and were lower in the model that included Gal-3 and sST2 compared to the model with only sST2 included. The group-based calibration showed that the models that predicted death were well-calibrated when the biomarkers were included. When predicting HF, the group-based calibration indicated that the only model that was well-calibrated was the model that included Gal-3. Regarding discrimination, the individual additions of Gal-3 and sST2 to the reference model slightly increased the C-statistic for the prediction of death and HF, as did the addition of Gal-3 to the model for death with sST2 included. In examining reclassification, of note is that adding Gal-3 to the model with sST2 showed improvement in classification as measured by the continuous NRI, especially for death. The nonevent NRI is the larger component of the continuous NRI, which might suggest that the addition of Gal-3 and sST2 to the model helps decrease the predicted risk for those who don’t experience the event more so than to increase the predicted risk for those who do experience the event.

DISCUSSION

Herein, we report on the value of Gal-3 for post MI risk stratification in a large non-selected community cohort. Our finding that, in a non-selected geographically defined cohort, Gal-3 is elevated in 34% of the patients presenting with an incident MI was unexpected. The large increase in the risk of death and HF with increasing levels of Gal-3 was striking, as it was independent of indicators of MI severity, of comorbidity and of sST2, which as we have previously shown is also associated with death and HF after MI. The dose-response pattern uncovered by the tertile analyses supports causality. Because these data represent the comprehensive experience of a community, they are of optimal clinical relevance and draw attention to new approaches for contemporary risk stratification after MI in clinical practice.

Importantly, troponin T levels were not associated with Gal-3 levels and the association between Gal-3 and outcomes was unchanged by the inclusion of troponin T in the models. This is important as troponin is a major prognostic indicator which serves as a marker of MI severity, reflecting the amount of myocardial necrosis. Gal-3 elevation reflects cardiac inflammation and fibrosis and thus different mechanistic pathways than troponin. It was thus logical to hypothesize that it would independently be associated with post MI outcomes. Our data provide robust evidence that this is the case by demonstrating a strong association between Gal-3 and outcomes which is independent of key clinical factors and troponin, and follows a dose-response pattern which supports causality. For HF, the association with Gal-3 was similar regardless of the type of HF (HFpEF or HFrEF). These data represent the comprehensive experience of a large contemporary MI population, thus supporting a potential use of Gal-3 measurement in clinical practice as a novel biomarker for post MI risk stratification.

Experimental data suggest that Gal-3 plays a role in cardiac fibrosis, which is important for the occurrence of adverse cardiac remodeling that precedes clinical HF (9,10). Gal-3 is highly expressed by macrophages in animal hypertrophied heart models and induces cardiac fibroblast proliferation and deposition of type I collagen, leading to fibrosis and pathological remodeling (10,33). In human studies, Gal-3 has been shown to be a predictor of EF and infarct size at 4 months after MI (34). With cardiac magnetic resonance, elevated Gal-3 levels were associated with adverse post MI LV remodeling at 6 months (35), and in patients with ST-elevation MI, Gal-3 was an independent predictor of LV remodeling at 1 and 6 months (36).

While previously suggested, the *prognostic role of Gal-3 in ACS* was not convincingly established. In a case-control study (37), Gal-3 levels were higher among MI cases, and Gal-3 was associated with 30-day mortality and HF after MI. Lisowska et al (12) reported that Gal-3 was associated with more severe coronary disease in patients with ischemic heart disease and was an independent predictor of death after MI. In a post hoc analysis of the CLARITY-TIMI 28 trial, an association between increasing Gal-3 levels and cardiovascular death or HF at 30-days has been reported (38), but was attenuated after adjusting for other prognostic factors. These studies all have notable limitations, including small sample size, heterogeneous design and adjustment approaches, and patient selection, which all compromise external validity and hinder inference. As most studies only reported short-term

outcomes, the long term prognostic value of Gal-3 was still undefined. The present study substantively augments previous reports by convincingly demonstrating that Gal-3 is associated with a large excess risk of adverse outcomes after MI, including death and HF, independently of major confounders, in a large prospective community cohort of patients with first MI followed for an extensive period.

Other Biomarkers Recommended for Post MI Risk Stratification

Troponin is the biomarker of choice for post MI risk stratification and, as underscored in the current AHA/ACC guidelines, the use of newer biomarkers should be considered if they provide additional prognostic information over and above that provided by troponin. For example, the AHA/ACC guidelines mention that measuring “especially B-type natriuretic peptide (BNP), may be reasonable to provide additional prognostic information” (Class of recommendation IIb; Level of Evidence: B). This recommendation is formulated only for NSTEMI, and no additional biomarker is mentioned for STEMI.

We recently reported on the value of sST2 to predict adverse outcomes after acute MI independently of troponin (7). Herein, Gal-3 provided incremental prognostic information over clinical indicators and sST2. Both Gal-3 and sST2 are considered markers of cardiac fibrosis. We recognized that the appropriate “multimarker” approach to predict outcomes after MI remains to be fully defined as also is the case for the evolving field of contemporary post MI risk stratification (6). In this context, our findings contribute to addressing this question by convincingly demonstrating the incremental prognostic value of Gal-3 over that of clinical prognostic indicators and other biomarkers.

Limitations and Strengths

Some limitations to our study should be acknowledged. As in any observational study, we cannot exclude residual confounding, but this is likely to have minimal impact as we adjusted for numerous relevant covariates known to affect the risk of adverse clinical events. We could not directly compare our data with natriuretic peptides, which were not measured. However, natriuretic peptides reflect different mechanistic pathways, and reports have indicated the independent association of Gal-3 and sST2 with outcomes after MI and in heart failure (39). In a case-control study of patients after ACS, Grandin et al have shown that patients with elevated Gal-3 and BNP levels were at the highest odds of developing HF, suggesting a potential incremental value of Gal-3 for assessment of HF risk after ACS (40). Moreover, there was a very weak pattern of correlation between Gal-3 and BNP which argues against confounding by BNP and further supports that the expression of these two proteins is mediated by different biological pathways. Lastly, our findings will need replication in racial and ethnic groups underrepresented in the cohort.

Our study has several notable strengths. We utilized the comprehensive data resources of the Rochester Epidemiology Project to examine the impact of Gal-3 on clinical outcomes after MI. We report on a large and contemporary community cohort of patients with a first MI validated by standardized criteria (1), prospectively enrolled with measurement of 2 novel markers of cardiac fibrosis, Gal-3 and sST2. We report for the first time on Gal-3 as an independent prognostic marker after MI in a community cohort of unselected patients, which

is of optimal clinical relevance. The focus on incident (first ever) MIs is important as the findings cannot by design reflect prior clinical ischemic damage. Finally, the use of rigorous risk prediction statistical methods substantially strengthens the inference that can be drawn from our results.

CONCLUSION

In this community cohort of patients with incident MI, elevated Gal-3 levels at the time of the MI were strongly associated with mortality and HF over a long period of follow-up independently of key clinical prognostic indicators and of troponin and sST2. The large excess risk of HF associated with Gal-3 does not differ by HF type, supporting its role in predicting HFrEF and HFpEF similarly. Our findings suggest a role for measuring Gal-3 levels for risk stratification post MI.

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ABBREVIATIONS and ACRONYMS

ACS	acute coronary syndrome
BNP	B-type natriuretic peptide
CV	cardiovascular
Gal-3	galectin-3
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
ICD	International Classification of Diseases
LV	left ventricle
sST2	soluble suppression of tumorigenicity 2

REFERENCES

1. Roger VL, Weston SA, Gerber Y, et al. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. Circulation 2010;121:863–9. [PubMed: 20142444]
2. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010;362:2155–65. [PubMed: 20558366]
3. Gerber Y, Weston SA, Jiang R, Roger VL. The changing epidemiology of myocardial infarction in Olmsted County, Minnesota, 1995–2012. Am J Med 2015;128:144–51. [PubMed: 25261010]

4. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation 2017;135:e146–e603. [PubMed: 28122885]
5. Cohn J, Ferrari R, Sharpe N. Cardiac remodeling- Concepts and clinical implications: A consensus paper from an international forum on cardiac remodeling. Journal of the American College of Cardiology 2000;35:569–582. [PubMed: 10716457]
6. Gerber Y, Weston SA, Enriquez-Sarano M, et al. Contemporary Risk Stratification After Myocardial Infarction in the Community: Performance of Scores and Incremental Value of Soluble Suppression of Tumorigenicity-2. J Am Heart Assoc 2017;6.
7. Jenkins WS, Roger VL, Jaffe AS, et al. Prognostic Value of Soluble ST2 After Myocardial Infarction: A Community Perspective. Am J Med 2017;130:1112 e9–1112 e15.
8. de Boer RA, Voors AA, Muntendam P, van Gilst WH, van Veldhuisen DJ. Galectin-3: a novel mediator of heart failure development and progression. Eur J Heart Fail 2009;11:811–7. [PubMed: 19648160]
9. Yu L, Ruifrok WP, Meissner M, et al. Genetic and pharmacological inhibition of galectin-3 prevents cardiac remodeling by interfering with myocardial fibrogenesis. Circ Heart Fail 2013;6:107–17. [PubMed: 23230309]
10. Sharma UC, Pokharel S, van Brakel TJ, et al. Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. Circulation 2004;110:3121–8. [PubMed: 15520318]
11. Weir RA, Petrie CJ, Murphy CA, et al. Galectin-3 and cardiac function in survivors of acute myocardial infarction. Circ Heart Fail 2013;6:492–8. [PubMed: 23505301]
12. Lisowska A, Knapp M, Tycinska A, et al. Predictive value of Galectin-3 for the occurrence of coronary artery disease and prognosis after myocardial infarction and its association with carotid IMT values in these patients: A mid-term prospective cohort study. Atherosclerosis 2016;246:309–17. [PubMed: 26828748]
13. O'Donoghue ML, Morrow DA, Cannon CP, et al. Multimarker Risk Stratification in Patients With Acute Myocardial Infarction. J Am Heart Assoc 2016;5.
14. Rocca WA, Yawn BP, St Sauver JL, Grossardt BR, Melton LJ, 3rd. History of the Rochester Epidemiology Project: half a century of medical records linkage in a US population. Mayo Clin Proc 2012;87:1202–13. [PubMed: 23199802]
15. St Sauver JL, Grossardt BR, Leibson CL, Yawn BP, Melton LJ 3rd, Rocca WA. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester Epidemiology Project. Mayo Clin Proc 2012;87:151–60. [PubMed: 22305027]
16. White AD, Folsom AR, Chambless LE, et al. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. J Clin Epidemiol 1996;49:223–33. [PubMed: 8606324]
17. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36:959–69. [PubMed: 10987628]
18. Dieplinger B, Januzzi JL Jr., Steinmair M, et al. Analytical and clinical evaluation of a novel high-sensitivity assay for measurement of soluble ST2 in human plasma--the Presage ST2 assay. Clin Chim Acta 2009;409:33–40. [PubMed: 19699192]
19. Broch K, Ueland T, Nymo SH, et al. Soluble ST2 is associated with adverse outcome in patients with heart failure of ischaemic aetiology. Eur J Heart Fail 2012;14:268–77. [PubMed: 22302661]
20. Daniels LB, Clopton P, Iqbal N, Tran K, Maisel AS. Association of ST2 levels with cardiac structure and function and mortality in outpatients. Am Heart J 2010;160:721–8. [PubMed: 20934567]
21. Pascual-Figal DA, Manzano-Fernandez S, Boronat M, et al. Soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide: complementary role for risk stratification in acutely decompensated heart failure. Eur J Heart Fail 2011;13:718–25. [PubMed: 21551163]

22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–83. [PubMed: 3558716]
23. Kors JA, Crow RS, Hannan PJ, Rautaharju PM, Folsom AR. Comparison of computer-assigned Minnesota Codes with the visual standard method for new coronary heart disease events. Am J Epidemiol. 2000;151:790–7. [PubMed: 10965976]
24. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. Circ Hart Fail. 2012;5:720–6.
25. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971;285:1441–6. [PubMed: 5122894]
26. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. JAMA 2004;292:344–50. [PubMed: 15265849]
27. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics−−2012 update: a report from the American Heart Association. Circulation 2012;125:e2–e220. [PubMed: 22179539]
28. Crowson CS, Atkinson EJ, Therneau TM. Assessing calibration of prognostic risk scores. Stat Methods Med Res 2016;25:1692–706. [PubMed: 23907781]
29. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–87. [PubMed: 8668867]
30. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Statistics in Medicine. 2011;30:11–21. [PubMed: 21204120]
31. Mayo Clinic Mayo Medical Laboratories. Test ID: GAL3 Galectin-3, Serum. https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/86202.
32. Coglianese EE, Larson MG, Vasan RS, et al. Distribution and clinical correlates of the interleukin receptor family member soluble ST2 in the Framingham Heart Study. Clin Chem 2012;58:1673–81. [PubMed: 23065477]
33. de Boer RA, Yu L, van Veldhuisen DJ. Galectin-3 in cardiac remodeling and heart failure. Curr Heart Fail Rep 2010;7:1–8. [PubMed: 20425490]
34. van der Velde AR, Lexis CP, Meijers WC, et al. Galectin-3 and sST2 in prediction of left ventricular ejection fraction after myocardial infarction. Clin Chim Acta 2016;452:50–7. [PubMed: 26528636]
35. Perea RJ, Morales-Ruiz M, Ortiz-Perez JT, et al. Utility of galectin-3 in predicting post-infarct remodeling after acute myocardial infarction based on extracellular volume fraction mapping. Int J Cardiol 2016;223:458–464. [PubMed: 27544605]
36. Di Tano G, Caretta G, De Maria R, et al. Galectin-3 predicts left ventricular remodelling after anterior-wall myocardial infarction treated by primary percutaneous coronary intervention. Heart 2017;103:71–77. [PubMed: 27465055]
37. Tsai TH, Sung PH, Chang LT, et al. Value and level of galectin-3 in acute myocardial infarction patients undergoing primary percutaneous coronary intervention. J Atheroscler Thromb 2012;19:1073–82. [PubMed: 23037954]
38. Calvier L, Martinez-Martinez E, Miana M, et al. The impact of galectin-3 inhibition on aldosterone-induced cardiac and renal injuries. JACC Heart failure 2015;3:59–67. [PubMed: 25458174]
39. Tunon J, Blanco-Colio L, Cristobal C, et al. Usefulness of a combination of monocyte chemoattractant protein-1, galectin-3, and N-terminal probrain natriuretic peptide to predict cardiovascular events in patients with coronary artery disease. Am J Cardiol 2014;113:434–40. [PubMed: 24295549]
40. Grandin EW, Jarolim P, Murphy SA, et al. Galectin-3 and the development of heart failure after acute coronary syndrome: pilot experience from PROVE IT-TIMI 22. Clin Chem 2012;58:267–73. [PubMed: 22110019]

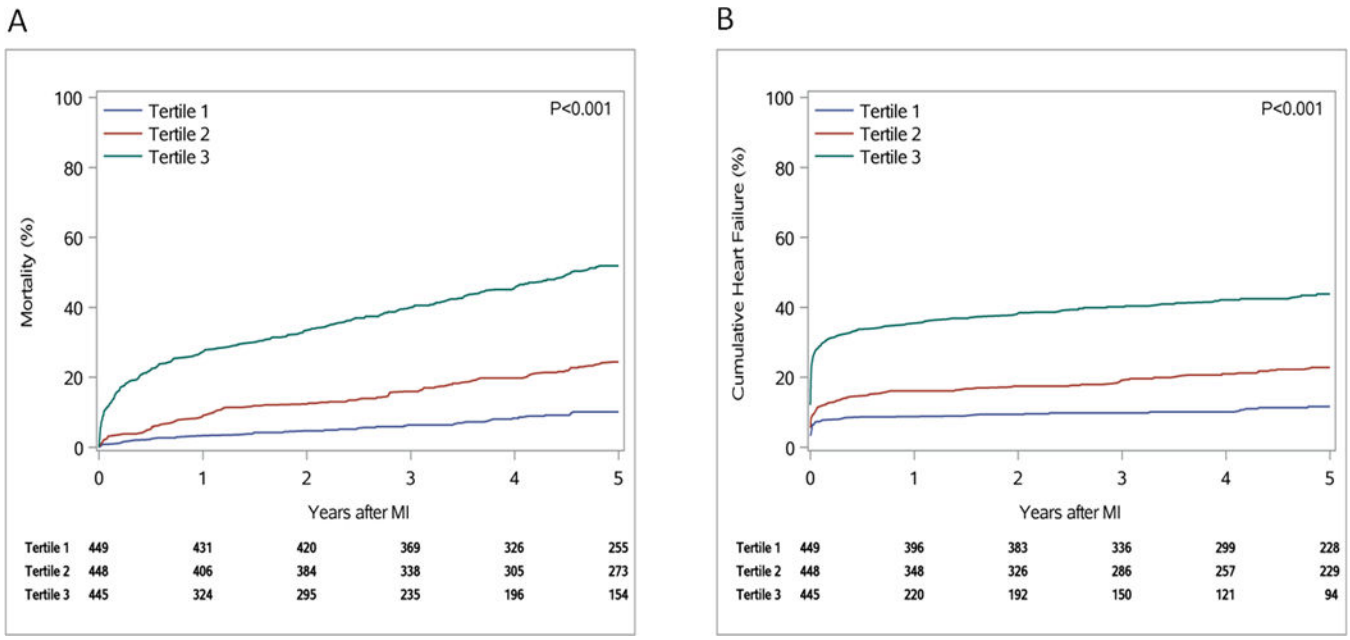
PERSPECTIVES

Competency in medical knowledge:

This is the first large prospective population-based study to demonstrate that elevated galectin-3 levels at the time of incident MI are a strong predictor of long-term mortality and heart failure independently of key clinical prognostic indicators and other biomarkers, including troponin and sST2.

Translational Outlook:

Further studies are warranted to better define the incremental role of Gal-3 over other biomarkers and its potential utilization in clinical practice for improving contemporary risk stratification after MI.



Central Illustration.

Cumulative incidence of death (A) and heart failure treating death as a competing risk (B) after incident myocardial infarction according to tertiles of Galectin-3. Number of subjects at risk over follow-up is presented by Galectin-3 tertile. MI indicates myocardial infarction.

TABLE 1.

Patient Characteristics by Tertiles of Galectin-3 at Time of Incident Myocardial Infarction

	Total (n=1342)	Gal-3 Tertile 1 (n=449)	Gal-3 Tertile 2 (n=448)	Gal-3 Tertile 3 (n=445)	P_{trend}
Age (years), mean (SD)	67.1 (14.9)	60.3 (13.3)	67.9 (14.2)	73.3 (14.4)	<0.001
Male sex	822 (61.3)	334 (74.4)	265 (59.2)	223 (50.1)	<0.001
Cardiovascular risk factors					
BMI, mean (SD)	28.9 (6.5)	29.2 (5.9)	28.8(6.3)	28.7 (7.2)	0.25
Current smoker	267 (19.9)	121 (26.9)	84 (18.8)	62 (13.9)	<0.001
Familial coronary disease	276 (20.7)	112 (25.2)	92 (20.6)	72 (16.3)	0.001
Diabetes mellitus	317 (23.6)	68 (15.1)	101 (22.5)	148 (33.3)	<0.001
Hypertension	942 (70.2)	247 (55.0)	322 (71.9)	373(83.8)	<0.001
Hyperlipidemia	882 (65.7)	273 (60.8)	306 (68.3)	303(68.1)	0.02
Comorbidities					
Prior HF	163 (12.1)	7 (1.6)	49(10.9)	107 (24.0)	<0.001
Cerebrovascular disease	177 (13.2)	28(6.2)	58 (12.9)	91 (20.4)	<0.001
History of malignancy	249 (18.6)	52 (11.6)	82 (18.3)	115 (25.8)	<0.001
Chronic obstructive pulmonary disease	211 (15.7)	37 (8.2)	79 (17.6)	95 (21.3)	<0.001
eGFR (mL/min per 1.73m^2),	61.4	68.1	61.6	48.3	<0.001
median (25th-75th percentile)	(48.4, 74.7)	(59.2, 81.4)	(52.0, 72.7)	(35.7, 64.7)	
Charlson comorbidity index,	1.0	0.0	1.0	3.0	<0.001
median (25th-75th percentile)	(0.0, 3.0)	(0.0, 1.0)	(0.0, 3.0)	(1.0, 5.0)	
MI characteristics					
Maximum troponin T (ng/mL), median (25th-75th percentile)	0.7 (0.2, 2.1)	0.9 (0.3, 2.5)	0.6 (0.2, 2.1)	0.5 (0.2, 1.8)	0.30
Non ST-elevation MI	1057 (78.8)	323 (71.9)	351 (78.3)	383(86.1)	<0.001
Q waves on ECG	660 (53.3)	205 (49.0)	207 (50.0)	248 (60.9)	0.001
Anterior MI	481 (35.8)	144 (32.1)	151 (33.7)	186 (41.8)	0.003
Killip class >1	287 (21.7)	59 (13.3)	74 (16.7)	154 (35.2)	<0.001
EF, mean (SD)	52.9 (12.5)	54.7 (10.4)	54.4 (11.1)	49.4 (15.1)	<0.001
ACE inhibitor/ARB at discharge	784 (60.8)	276 (61.7)	280 (63.5)	228 (56.9)	0.16
Beta blocker at discharge	1101 (85.4)	403 (90.2)	370 (83.9)	328 (81.8)	0.001

Data are presented as n (%) unless otherwise specified.

ACE denotes angiotensin-converting enzyme; ARB, Angiotensin II receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ECG, electrocardiogram; EF, ejection fraction within 30 days after MI; eGFR, estimated glomerular filtration rate; Gal-3, galectin-3; HF, heart failure; MI, myocardial infarction.

TABLE 2.

Hazard Ratios (95% Confidence Intervals) Associated With Galectin-3 for Outcomes after Incident Myocardial Infarction

	Gal-3 Tertile 1 (n=449)	Gal-3 Tertile 2 (n=448)	Gal-3 Tertile 3 (n=446)	P_{trend}	10-unit increase in Gal-3	*P*
Death (n=484)						
Unadjusted	1.0	2.28 (1.70–3.05)	6.02 (4.59–7.90)	<0.001	1.41 (1.36–1.46)	<0.001
Model 1 *	1.0	1.58 (1.17–2.13)	3.24 (2.43–4.33)	<0.001	1.40 (1.34–1.46)	<0.001
Model 2 †	1.0	1.26 (0.93–1.70)	2.35 (1.76–3.15)	<0.001	1.30 (1.24–1.36)	<0.001
Cardiovascular death (n=188) §						
Unadjusted	1.0	2.99 (1.82–4.90)	7.04 (4.40 −11.25)	<0.001	1.37 (1.29–1.46)	<0.001
Model 1 *	1.0	1.89 (1.14–3.14)	3.27 (2.00–5.37)	<0.001	1.35 (1.26–1.45)	<0.001
Model 2 †	1.0	1.56 (0.94–2.58)	2.29 (1.39–3.77)	<0.001	1.26 (1.17–1.36)	<0.001
Heart Failure (n=368)						
Unadjusted	1.0	2.28 (1.65–3.16)	5.54 (4.09–7.51)	<0.001	1.29 (1.23–1.34)	<0.001
Model 1 *	1.0	1.70 (1.22–2.37)	3.46 (2.51–4.78)	<0.001	1.25 (1.19–1.32)	<0.001
Model 2 ‡	1.0	1.40 (1.00–1.96)	2.25 (1.61–3.15)	<0.001	1.15 (1.09–1.22)	<0.001
HFrEF (n=177) ?						
Unadjusted	1.0	1.86 (1.17–2.96)	5.16 (3.39–7.85)	<0.001	1.29 (1.22–1.37)	<0.001
Model 1 *	1.0	1.52 (0.94–2.44)	3.70 (2.37–5.76)	<0.001	1.27 (1.19–1.35)	<0.001
Model 2 ‡	1.0	1.29 (0.80–2.08)	2.30 (1.46–3.66)	<0.001	1.16 (1.08–1.25)	<0.001
HFpEF (n=138) ?						
Unadjusted	1.0	2.23 (1.32–3.76)	5.46 (3.35–8.89)	<0.001	1.27 (1.18–1.36)	<0.001
Model 1 *	1.0	1.57 (0.92–2.67)	3.10 (1.85–5.21)	<0.001	1.23 (1.12–1.34)	<0.001
Model 2 ‡	1.0	1.36 (0.80–2.34)	2.29 (1.34–3.92)	0.001	1.14 (1.04–1.26)	0.007

* Adjusted for age and sex.

† Adjusted for age, sex, Charlson comorbidity index and maximum troponin T.

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‡ Adjusted for age, sex, Charlson comorbidity index, maximum troponin T and history of HF prior to the index MI.

§ 8 patients are missing cause of death.

? 56 patients with HF are missing EF.

Gal-3 denotes galectin-3; HFrEF HF with reduced EF; HFpEF HF with preserved EF.

TABLE 3.

Prognostic Value of Galectin-3 in Predicting Death and Heart Failure after Incident Myocardial Infarction

Model	Reference model*	Reference model + Gal-3	Reference model + sST2	[Reference model + sST2] + Gal-3
Death				
Calibration				
Likelihood ratio test	-	$P<0.001^{\dagger}$	$P<0.001^{\dagger}$	$P<0.001^{\ddagger}$
AIC	5951.6	5857.3	5829.0	5784.8
BIC	5972.5	5882.4	5854.1	5814.1
Group-based calibration	P=0.009	P=0.20	P=0.64	P=0.61
Discrimination				
C-statistic (95% CI)	0.79 (0.77–0.81)	0.81 (0.79–0.84)	0.82 (0.80–0.84)	0.83 (0.81–0.85)
Reclassification				
Continuous NRI (95% CI)	-	0.40 (0.27–0.55)	0.59 (0.50–0.66)	0.36(0.22–0.44)
Event NRI (95% CI)	-	0.08 (−0.01–0.19)	0.16 (0.10–0.23)	0.08(−0.02–0.13)
Nonevent NRI (95% CI)	-	0.32 (0.28–0.40)	0.43 (0.38–0.48)	0.28(0.16–0.38)
Heart failure				
Calibration				
Likelihood ratio test		$P<0.001^{\dagger}$	$P<0.001^{\dagger}$	$P<0.001^{\ddagger}$
AIC	4733.1	4703.7	4671.2	4661.1
BIC	4756.6	4731.1	4698.6	4692.3
Group-based calibration	P=0.03	P=0.31	P=0.03	P=0.006
Discrimination				
C-statistic (95% CI)	0.76 (0.74–0.79)	0.77 (0.75–0.80)	0.79 (0.77–0.81)	0.80 (0.77–0.82)
Reclassification				
Continuous NRI (95% CI)	-	0.32 (0.20–0.40)	0.48 (0.35–0.60)	0.17 (0.09–0.27)
Event NRI (95% CI)	-	0.10 (0.03– 0.13)	0.16 (0.08–0.23)	0.02 (−0.01–0.08)
Nonevent NRI (95% CI)	-	0.22 (0.18–0.28)	0.31 (0.23–0.37)	0.14 (0.06–0.19)

*Reference model for death includes age, sex, Charlson comorbidity index and maximum troponin T. Reference model for heart failure includes age, sex, Charlson comorbidity index maximum troponin T, and heart failure prior to myocardial infarction.

†Compared to reference model.

‡Compared to reference model + sST2.

AIC denotes Akaike information criterion; BIC, Bayesian information criterion; CI, confidence interval; Gal-3, galectin-3; NRI, net reclassification index; sST2, soluble suppression of tumorigenicity-2.