Observational Study

Medicine®

OPEN

Role of galectin-3 and plasma B type-natriuretic peptide in predicting prognosis in discharged chronic heart failure patients

Mauro Feola (MD, FESC)[a,*], Marzia Testa (MD)[b], Laura Leto (MD)[b], Marco Cardone (MD)[c], Mario Sola (MD)[c], Gian Luca Rosso (MD)[d]

Abstract

Galectin-3 demonstrated to be a robust independent marker of cardiovascular mid-term (18-month) outcome in heart failure (HF) patients. The objective of this study was to analyze the value of a predischarged determination of plasma galectin-3 alone and with plasma brain natriuretic peptide (BNP) in predicting mid-term outcome in frequent-flyers (FF) HF (≥2 hospitalization for HF/year)/dead patients discharged after an acute decompensated HF (ADHF) episode.

All FF chronic HF subjects discharged alive after an ADHF were enrolled. All patients underwent a determination of BNP and galectin-3, a 6-minute walk test, and an echocardiogram within 48 hours upon hospital discharge. Death by any cause, cardiac transplantation, and worsening HF requiring readmission to hospital were considered cardiovascular events.

Eighty-three patients (67 males, age 73.2 ± 8.6 years old) were analyzed (mean follow-up 11.6 ± 5.2 months; range 4–22 months). During the follow-up 38 events (45.7%) were scheduled: (13 cardiac deaths, 35 rehospitalizations for ADHF). According to medical history, in 33 patients (39.8%) a definition of FF HF patients was performed (range 2–4 hospitalization/year). HF patients who suffered an event (FF or death) demonstrated more impaired ventricular function ($P = 0.037$), higher plasma BNP ($P = 0.005$), and Gal-3 at predischarge evaluation ($P = 0.027$). Choosing adequate cut-off points (BNP ≥ 500 pg/mL and Gal-3 ≥ 17.6 ng/mL), the Kaplan–Meier curves depicted the powerful stratification using BNP + Gal-3 in predicting clinical course at mid-term follow-up (log rank 5.65; $P = 0.017$).

Adding Gal-3 to BNP, a single predischarge strategy testing seemed to obtain a satisfactorily predictive value in alive HF patients discharged after an ADHF episode.

Abbreviations: ADHF = acute decompensated heart failure, BNP = brain natriuretic peptide, FF = frequent-flyers, HF = heart failure, LOS = length of hospital stay, LVEF = left ventricle ejection fraction, NYHA = New York Heart Association.

Keywords: b type-natriuretic peptide, chronic heart failure, galectin-3, prognosis

1. Introduction

Risk stratification in patients suffering from heart failure (HF) is based on a variety of clinical and laboratory variables. Indeed, several prognostic parameters have been identified, including age, New York Heart Association (NYHA) class, renal function, comorbidity such as atrial fibrillation, diabetes mellitus, and ischemic heart disease.[1] In acute decompensated heart failure (ADHF) episodes, the degree of renal dysfunction and arterial hypotension easily stratified patients with worst clinical outcome.[2] A single determination of brain natriuretic peptide (BNP) plasma level represents a reliable risk stratification procedure and its increase is considered a sensitive diagnostic marker of left ventricular dysfunction[3–4] having a clear prognostic relevance in predicting cardiovascular events in HF patients.[5–7] In discharged HF patients the combination of galectin-3 and NT-proBNP seemed to be the best predictor for short-term (60-day) mortality in the PRIDE study.[8] Furthermore, in the substudy of COACH[9] galectin-3 demonstrated to be a robust independent marker of cardiovascular mid-term (18-month) outcome in HF patients with much stronger relevance in patients with preserved left ventricular ejection fraction (LVEF) in comparison with reduced LVEF. Finally, Shah et al[10] documented as a single determination of galectin-3 during an ADHF hospitalization predicted mortality (in 63% being above the median value) in a longer follow-up (4-year) independently of echocardiographic parameters of HF severity.

Advanced HF patients constitute a challenge for cardiologists according to their high mortality and rehospitalization rate.[11,12] Therefore, a strategy for stratify planning tailored clinical follow-up in those patients seems to be mandatory.

The objective of this study was to analyze the value of a single, predischarged determination of plasma galectin-3 alone and in

Editor: Leonardo Gilardi.

The authors report no conflicts of interest.

[a] Cardiovascular Rehabilitation-Heart Failure Unit, Ospedale SS Trinità Fossano, [b] School of Geriatry, Università degli Studi Torino, [c] Laboratory Service Ospedale Mondovì, [d] Medical Emergency Service, ASL CN1-Cuneo, Italy.

[*] Correspondence: Feola Mauro, Cardiovascular Rehabilitation-Heart Failure Unit, Ospedale SS Trinità Fossano, Via Ospedale 4, 12045 Fossano Italy (e-mail: m_feola@virgilio.it).

Medicine (2016) 95:26(e4014)

Received: 23 April 2016 / Received in final form: 25 May 2016 / Accepted: 1 June 2016

http://dx.doi.org/10.1097/MD.0000000000004014

correlation with plasma BNP in predicting mid-term clinical outcome in worst clinical outcome [frequent-flyers (FF) + death] chronic HF patients discharged after an ADHF episode.

2. Methods

All chronic HF subjects discharged after an acute episode of cardiac decompensation were enrolled in an out-patient clinic follow-up. Patients were classified as having CHF according to the criteria commonly accepted in literature,[13] namely the presence of 2 major criteria or 1 major criterion +2 minor criteria according to the Framingham score and an NYHA functional class II, III, or IV, due to an exacerbation of symptoms with at least 1 class deterioration. The presence of inadequate echo images or no adherence to the therapy and disagreement with the periodical follow-up were considered exclusion criteria. All patients underwent a clinical examination, a 12-lead electrocardiogram, plasma determination of BNP, water composition (on admission and at discharge), 6-minute walk test, noninvasive cardiac output, and a transthoracic echocardiogram within 48 hours upon hospital discharge. The criteria for discharging HF patients were the following: subjective improvement on the basis of NYHA class, with no orthopnea; $90 < SBP < 120$ mm Hg; heart rate < 100 bpm; pulse oxymetry in ambient air $> 90\%$; and diuresis > 1000 mL/day.[11] Serum creatinine was checked on clinical stability. According to the study protocol, HF outpatients were checked at 3 and 6 months after discharge. In case of worsening of the clinical status (worsening dyspnea, body weight increase or edema, and cardiac arrhythmias), a clinical control was provided. The therapy prescribed in those patients included angiotensin-converting enzyme inhibitors (enalapril, ramipril), angiotensin receptor blockade (valsartan) in case of enalapril/ramipril intolerance, beta-blockers (bisoprolol), digoxin, loop diuretic, and spironolactone at low dose. For beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockade, the patients' maximum tolerated dose was used, after an adequate titration period.

Echocardiograms were performed with a Vivid 7 computed sonography system (GE Medical Systems, Waukesha, WI) according to the recommendations of the American Society of Echocardiography.[14] Two-dimensional apical 2- and 4-chamber views were used for volume measurements; left ventricle ejection fraction (LVEF) was calculated with a modified Simpson method using biplane apical (2- and 4-chamber) views. The left ventricle (LV) end-diastolic volume and the LV end-systolic volume were recorded. All the echo examinations were performed by expert operators blinded to the results of BNP assay; the intraobserver variability in the evaluation of LVEF was found to be $<5\%$. Echocardiographic measurements, including LV end-diastolic diameter and the diastolic thickness of the ventricular septum and the posterior LV wall, were determined according to the American Society Echocardiography recommendations.[15] Systolic dysfunction was defined as a level of LVEF $< 50\%$. The definition of restrictive filling pattern (grade 3) was a predefined modification of classifications used in prior studies[15]: E/A ≥ 2, DT ≤ 150 msec, S/D ratio < 1, and AR > 35 cm/sec. All these criteria should be verified to define the restrictive filling pattern. The other diastolic filling patterns were classified as: grade 1 (abnormal relaxation) when E/A < 1 with a DT > 240 ms; grade 2 (pseudonormal) when E/A between 0.75 and 1.5, DT between 160 and 240 ms and finally E/Ea > 15.[15] The Doppler sample was set 1 to 2 mm under the free edges of the mitral valve using the apical 4-chamber projection; an average of 5 beats was considered. In patients suffering from atrial fibrillation at the time of the echocardiogram, the diastolic function was classified as: restrictive pattern (DT ≤ 150 msec) or indeterminate (DT > 150 msec). The presence of this diastolic pattern with an LVEF $> 50\%$ was defined as an isolated diastolic dysfunction. The tricuspid annular plane systolic excursion was measured in a 4-chamber view by placing the 2D cursor at the tricuspid lateral annulus and measuring the distance of systolic annular RV excursion along a longitudinal line defining the end of systole as the end of the T wave in the electrocardiogram. Systolic right ventricular (or pulmonary artery) pressure was calculated using the modified Bernoulli equation: PAP $= 4 \times$ (tricuspid systolic jet)$^2 + 10$ mm Hg (estimated right atrial pressure).

Whole blood was obtained from subjects via standard venipuncture just before discharging, when patients were considered stabilized after an acute HF admission. Serum was isolated within 60 minutes of sampling, shipped overnight refrigerated and stored at $-70°$ colder until the time of testing. Galectin-3 was analyzed used an ELISA (BG Medicine). This assay has a lower limit of detection of 1.13 μg/L and demonstrated no cross-reactivity with other galectins or collagens.[16] Total imprecision of the assay at concentration of 17.6 and 26.3 μg/L is 5.1% and 4.2%, respectively. The bedside Triage B type natriuretic fluorescence immunoassay (Alere Diagnostics, CA) was also used in all population studied. The Triage Meter is used to measure BNP concentration by detecting a fluorescent emission that reproduces the amount of BNP in the blood. A total of 250 μL of whole blood was added to the disposable device, then the cells were filtered and separated from the plasma with BNP, which entered a reaction chamber, containing fluorescent BNP antibodies. After 2-minute incubation, the BNP–antibody mixture migrated to an area containing immobilized antibodies and remained fixed. The unbound fluorescent antibodies were washed away by the excess sample fluid. Then, the Triage Meter measured the fluorescent intensity of the BNP assay area. The assay results were complete in 15 minutes. Performance characteristics of the test: assay range 5 to 5000 pg/mL; total CV 9.2% to 11.4%.

Death by any cause, cardiac transplantation, and worsening HF requiring readmission to the hospital were considered cardiovascular events. Data regarding the occurrence of cardiovascular events were collected from multiple sources in all patients (follow-up consultations or phone calls). FF HF patient was defined who underwent ≥2 hospitalization for HF for year. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki; an informed consent was required for every patients and our local Ethic Committee approved this study.

2.1. Statistical analysis

Descriptive statistics were used to report the prevalence of various parameters. Categorical data were presented as numbers (percent), continuous data as mean ± standard deviation (SD) for normally distributed variables. The Shapiro–Wilk test was used to evaluate whether or not the distribution of the variables was normal. The mean values of any 2 groups were compared using the Student t test and the means of more 2 groups were assessed using Analysis of Variance followed by the Bonferroni multiple-comparison test. The Pearson χ^2 test and the Fischer exact test were used for comparing categorical variables (NYHA class, cardiovascular events). The Spearman rank-order correlation coefficient (rho) was used to measure the strength and

direction of association between galectin-3 and glomerular filtrate and between galectin-3 and BNP. Event-free survival was estimated by Kaplan–Meier method, and curves were compared with the log-rank test. A P value < 0.05 was considered significant. All statistical calculations were performed on STATA software (version 11.0 STATA Corporation, College Station, TX).

3. Results

Eighty-three patients (67 males, age 73.2 ± 8.6 years old) were discharged after a new diagnosis of CHF or for acute decompensation in chronic CHF and were requested to enter the study, signing an informed consent and were enrolled (mean follow-up 11.6 ± 5.2 months; range 4–22 months). The etiology of HF was interpreted as: 35 ischemic (42.1%), 23 cardiomyopathy (28%), 22 hypertensive (26.5%), and finally 3 others (3.6%). During the follow-up 48 events (57.8%) were scheduled (13 cardiac deaths, 35 rehospitalizations for HF). Twenty-eight HF patients were hospitalized ≥2 times/year (range 2–4 times/year) and were defined FF (8 patients out of 28 died because of a cardiac death). Therefore, the group with a worst clinical prognosis (FF + cardiac death) was formed by 33 patients (39.8%). Main differences between the events group versus control group are described in Table 1. Although the events group population seemed to be not older or hyponatremic, the predischarge value of galectin-3 and plasma BNP were significantly higher ($P = 0.027$ and 0.005, respectively). In HF patients with worst clinical outcome a more severe impairment in LV systolic function ($P = 0.0037$) emerged, without a significant LV enlargement or a right ventricular involvement. However, the diastolic filling pattern evaluated with echocardiography seemed to be not different in the 2 groups. At univariate analysis, a negative Spearman coefficient (rho) of −0.38 indicates a moderate decreasing monotonic trend between galectin-3 and glomerular filtrate ($P = 0.0055$), while a positive correlation (rho = 0.44, $P = 0.002$) between galectin-3 and BNP was detected. At multivariate analysis, only galectin-3 showed a significant correlation with worst clinical prognosis ($P = 0.047$; odds ratio 1.05, confidence interval 1.001–1.10), independently to age and renal function, being for each galectin-3 increment of 1 ng/mL determined an increase of 5% in probability of cardiovascular events. Choosing adequate cut-off points, the Kaplan–Meier curves depicted the powerful stratification using a galectin-3 level of 17.6 pg/mL (Fig. 1) added to plasma BNP level of 500 pg/mL (log rank 5.65; $P = 0.017$).

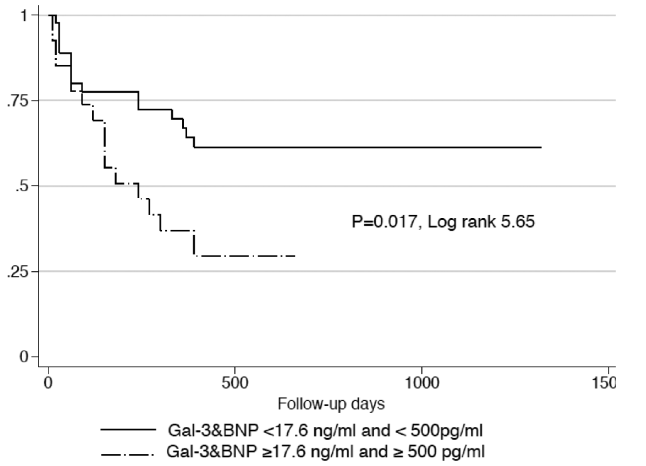

Figure 1. the Kaplan–Meier event-free curve (with the log-rank) according to the selected cut-off values for galectin-3 (17.6 ng/mL) and brain natriuretic peptide (BNP) (500 pg/mL).

4. Discussion

Elderly patients with chronic HF represent most of subjects (70%) admitted to hospitals for acute cardiac decompensation; the length of hospitalization lasts usually >2 weeks in geriatric wards and readmissions are frequent.[17] Recently, the OPTIMIZE-HF study[11] included more than 30,000 HF patients discharged from 215 hospitals, described a short length of hospitalization (4 days) but a 21.3% of rate of readmission within 30-day. This study evidenced as an early (1-week) outpatient clinical follow-up after discharged helped HF patients

Table 1

Differences between main parameters in event group (FF + death) versus control group.

	Control group (50 pts)	FF + death (33 pts)	*P*
Age	73.8 ± 6.9	72.8 ± 11.5	0.6
Sodium, MEq/L	140 ± 3.5	140.1 ± 3.2	0.9
Galectin-3, pg/mL	19.4 ± 10.3	24.8 ± 11.2	0.027
LVEF, %	40.7 ± 15.8	32.9 ± 16.2	0.037
LVESD, mm	44.8 ± 14.9	49 ± 17.9	0.3
LVEDD, mm	58.7 ± 12.9	60.5 ± 11.3	0.5
TAPSE, mm	17.9 ± 4.3	16.9 ± 5.1	0.4
PAP, mm Hg	38.1 ± 10	38.9 ± 9.2	0.7
Creatinine	1.29 ± 0.9	1.3 ± 0.9	0.6
Atrial fibrillation	22 (44%)	17 (51.5%)	0.5
Diastolic pattern (I/II/III)	28/16/6	18/10/5	0.8
6MinWT, m	362.3 ± 119.7	302.9 ± 87.1	0.09
GFR	68.7 ± 17.9	60.2 ± 23.1	0.1
LOS, days	11.9 ± 6.6	10.6 ± 5.4	0.3
Hb, g/dL	13.1 ± 6.1	12.8 ± 2.1	0.7
BNP, pg/mL	725.1 ± 594.3	1391.17 ± 1288.5	0.005

BNP = brain natriuretic peptide, FF = frequent-flyers, GFR = glomerular filtration rate, Hb = hemoglobin level, LOS = length hospital stay, LVEDD = left ventricular diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, 6minWT = 6 minute walking test, PAP = pulmonary artery pressure, TAPSE = tricuspid annular plane systolic excursion.

to undergo to a lower probability to be readmitted within 30-day. In the IN-HF outcome, an Italian nationwide registry, the 30-day mortality after discharging for an acute episode of HF proved to be 2.8% and hospital readmission 6.2%.[12] Older age, longer in-hospital stay, the necessity of inotrope use, and worsening NYHA class identified HF patients discharged home who are at highest risk of death or readmission. Multiple interventions such as patients education, discharge planning, complete adherence to a correct and tailored medical therapy, scheduling follow-up after discharge, attention to caregivers, and follow-up telephone calls might be useful in reducing the 30-day risk of readmission and, generally, more comprehensive interventions reported greater success.[18] According to the huge number of HF patients discharged from our hospitals, easy and practical prognostic parameters able to predict adverse outcome are mandatory in order to allocate correctly our resources and established tailoring specific follow-up.

The analysis of this single-center HF clinic experience demonstrates as in older systolic HF patients discharged after an ADHF episode, the single determination of galectin-3 and BNP permitted to predict worst clinical outcome (death or multiple hospital admissions) at mid-term (11 months) follow-up. Galectin-3 is a lectin secreted in plasma usually at low levels but increased substantially the secretion under conditions like injury or stress, having a biological role in cell adhesion, inflammation, and above all, tissue fibrosis.[19] A single value of galectin-3 in patients admitted for an episode of ADHF clearly demonstrated a powerful prognostic power in predicting mortality and rehospitalization at short- or long-term follow-up.[8–10] On the contrary, a low plasma level of galectin-3 (<11.8 ng/mL) proved to be an independent predictor (odds ratio 20.9; $P=0.003$) for the absence of mortality and rehospitalization at a short-term follow-up (6 months) suggesting that a reclassification of the alive HF patients at discharge might help in planning an adequate clinical follow-up.[20] However, NT-ProBNP did not add an incremental value in order to predict low-risk events outcome postulating as natriuretic peptide, exploring hemodynamic loading conditions, might be less specific in detecting HF patients with favorable outcome. Moreover, the pooled analysis of 3 clinical trials including 902 HF patients[21] demonstrated as HF patients with galectin-3 >17.8 pg/mL had more risk (2.6–3 times) to be readmitted for ADHF from 30 to 120 days after discharge.

In our experience, none of other demonstrated parameters (renal function, length of hospital stay [LOS], and hemoglobin) seemed to correlate with an unfavorable outcome. In particular, the LOS was not different in the 2 groups, being prolonged (>10 days) according to the older age and the presence of comorbidity in a real-world population. In fact, while in OPTIMIZE-HF[11] the LOS was documented very short, in IN-HF outcome,[12] based on data coming from Cardiology Department, a prolonged LOS (10 days) emerged and significantly correlated with the risk of 30-day readmission. Data coming from the EVEREST Trial[22] suggested as a longer LOS was associated with cardiovascular and all cause hospital admissions, but indicated a lower risk of HF readmissions for HF within 30 days after discharging. In our experience, the limited series and the prolonged LOS did not permit to observe an influence by LOS in clinical outcome.

Finally, in a paramount of interesting predicting parameters in HF, clinicians should concentrate their attention on the most specific and cheapest at the moment of discharging your patients. Therefore, chronic HF patients discharged alive after an ADHF with an elevated predischarge value of galectin-3 (≥ 17.6 ng/mL) together with BNP (≥ 500 pg/mL) might be inserted into a rigid clinical follow-up, performed by the general practitioner or the HF out-clinic ambulatory, providing a strict control of body weight, hydration status, pharmacological adherence, and clinical status in order to prevent multiple readmissions.

5. Limitations

The main limitation of this study was the small sample size observed that might reduce the power of some consolidated prognostic parameters (as renal function). Moreover, the sample size did not permit a correct distinction between HFrEF and HFpEF. Finally, the risk of multiple rehospitalization for HF has normally correlated to the severity of cardiac condition as well as other nontested patient-related factors (social status, cognitive performance, and presence/absence of caregiver) that might significantly influence the rate of readmissions. In fact, it has been documented[23] in the DIG TRIAL, as about 58% of the nation variations in hospital readmission were correlated with socio-economic factors.

References

[1] Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the Task Force for the Diagnosis and Treatment of chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:1115–40.

[2] Fonarow GC, Adams KF, Abraham WT, et al. Risk stratification for in-hospital mortality in acutely decompensated heart failure. JAMA 2005;293:572–80.

[3] Boland DG, Abraham WT. Natriuretic peptides in heart failure. Congestive Heart Fail 1998;4:23–33.

[4] McDonagh TA, Robb SD, Murdoch DR, et al. Biochemical detection of left-ventricular systolic dysfunction. Lancet 1998;351:9–13.

[5] Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161–7.

[6] Berger R, Huelsman M, Strecker K, et al. B-type Natriuretic Peptide predicts sudden death in patients with chronic heart failure. Circulation 2002;105:2392–7.

[7] Feola M, Aspromonte N, Canali C, et al. Prognostic value of plasma brain natriuretic peptide, urea nitrogen and creatinine in outpatients >70 years of age with heart failure. Am J Cardiol 2005;965:705–9.

[8] Van Kimmenade RR, Jannuzzi JL, Ellinor PT, et al. Utility of amino-terminal pro-brain natriuretic peptide, galectin-3 and apelin for the evaluation of patients with acute heart failure. J Am Coll Cardiol 2006;48:1217–24.

[9] De Boer RA, Lok DJA, Jaarsma T, et al. Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction. Ann Med 2011;43:60–8.

[10] Shah RV, Chen-Tournoux AA, Picard MH, et al. Galectin-3, cardiac structure and function and long-term mortality in patients with acutely decompensated heart failure. Eur J Heart Fail 2010;12:826–32.

[11] Hernandez AF, Greiner MA, Fonarow GC, et al. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. JAMA 2010;303:1716–22.

[12] Di Tano G, De Maria R, Gonzini L, et al. The 30-day metric in acute heart failure revisited: data from IN-HF Outcome, an Italian nationwide cardiology registry. Eur J Heart Fail 2015;1710:1032–41.

[13] Peacock WF. Rapid optimization: strategies for optimal care of decompensated congestive heart failure patients in the emergency department. Rev Cardiovasc Med 2003;3:S41–8.

[14] Sahn DJ, Demaria A, Kisslo J, et al. The committee on M mode standardisation of the American Society of Echocardiography: recommendations regarding quantification in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072–83.

[15] Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. J Am Coll Cardiol 1998;32:865–75.

[16] Christenson RH, Duh S-H, Wu AH, et al. Multi-center determination of galectin-3 assay performance characteristics: anatomy of a novel assay for use in heart failure. Clin Biochem 2010;43:683–90.

[17] Di Lenarda A, Scherillo M, Maggioni AP, et al. Current presentation and management of heart failure in cardiology and internal medicine hospital units: a tale of words. The Temistocle study. Am Heart J 2003;146:E12.
[18] Ziaeian B, Fonarow GC. The prevention of hospital readmissions in heart failure. Prog Cardiovasc Dis 2016;58:379–85.
[19] Henderson NC, Sethi T. The regulation of inflammation by galectin-3. Immunol Rev 2009;230:160–71.
[20] Meijers WC, de Boer RA, van Veldhuisen DJ, et al. Biomarkers and low risk in heart failure. Data from COACH and TRIUMPH. Eur J Heart Fail 2015;17:1271–82.
[21] Meijers WC, Jannuzzi JL, deFilippi C, et al. Elevated plasma galectin-3 is associated with near-term rehospitalisation in heart failure: a pooled analysis of 3 clinical trials. Am Heart J 2014;167: 853–60.
[22] Khan H, Greene SJ, Fonarow GC, et al. Length of hospital stay and 30-day readmission following heart failure hospitalization: insights from the Everest trial. Eur J Heart Fail 2015;17:1022–31.
[23] The Digitalis Intervention GroupThe effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336: 525–35.