THE IMPORTANCE OF BIOMARKERS IN THE MANAGEMENT OF PATIENTS WITH HEART FAILURE AND PRESERVED EJECTION FRACTION

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Abstract: *Patients with heart failure (HF) can be divided into those with heart failure and a reduced ejection fraction (HFrEF) and those with heart failure and a preserved ejection fraction (HFpEF). In the presence of compromised systolic function, appropriate signs and symptoms make it relatively easy to set the diagnosis of heart failure. However, because of the nonspecific nature of clinical findings, especially the symptoms of heart failure, when left ventricle (LV) systolic functions normally, the diagnosis becomes more difficult. Efficient diagnosis and optimal therapy remain challenging in this population. Imaging, electrocardiographic, and circulating biomarkers, as well as pharmacogenetics, may help facilitating HF diagnosis, stratifying the risk, and individualizing the therapy. Biomarkers reflect myocyte stress, myocyte injury, renal function, systemic inflammation and fibrosis have contributed to better understanding the pathophysiologic mechanisms relevant to HFpEF, and may eventually help facilitating more effective and personalized management of this syndrome. Biomarkers include proteins, peptides, and microRNAs that can be measured in the plasma and can be shown to represent changes in myocardial structure or function that reflect underlying pathophysiologic processes.(1) In this article, we present the biomarkers that cause changes in hemodynamic and fibrosis in patients with HFpEF: natriuretic peptides, markers of extracellular matrix turnover, galectin-3, markers of renal function, cardiac troponins, ST2, growth differentiation factor (GDF-15), microRNAs.*

Approximately 40 to 50 % of patients with heart failure (HF) have a normal or nearly normal left ventricular ejection fraction (EF).(2) HF with reduced EF (HF-REF) and HF with preserved EF (HF-PEF) are distinct entities or part of a single spectrum which remains a matter of debate.(3,4)

Diastole is the period cardiac cycle between aortic valve closure and mitral valve closure and is divided in four phase: isovolumetric relaxation, early rapid ventricular filling, a period of low filling (diastasis) and late rapid filling during atrial contraction.

Progress in the management of HF-PEF has been thwarted by limited understanding of the relevant pathophysiologic mechanisms. The majority of patients with HF-PEF exhibit abnormalities of active myocardial relaxation and passive ventricular stiffness that contribute to abnormal ventricular filling in diastole.

Isolated diastolic dysfunction is the impairment of isovolumetric ventricular relaxation and decreased compliance of the left ventricle. With diastolic dysfunction, the heart is able to meet the body's metabolic needs, whether at rest or during exercise, but at a higher filling pressure. Transmission of higher end-diastolic pressure to the pulmonary circulation may cause pulmonary congestion, which leads to dyspnea and subsequent right heart failure. In severe cases, the ventricle becomes so stiff that the atrial muscle fails and end diastolic volume cannot be normalized with elevated filling pressure. This process reduces stroke volume and cardiac output causing effort intolerance.(5)

Hypertension and cardiac ischemia are the most common causes of HFEFp.(6) Concentric remodelling and hypertrophy of the ventricle as well as progressive myocardial fibrosis, particularly in patients with longstanding hypertension, are a hallmark of the disease and may be the key substrate for myocardial dysfunction in systole and diastole.(7)

In the context of the phenotypic and pathophysiologic abnormalities that have been observed, several circulating biomarkers may be relevant to the diagnosis, risk stratification, and treatment of HFEFp, including circulating neurohormones, markers of fibrosis and collagen turnover, and markers of inflammation.

Natriuretic Peptides

The best characterized biomarkers in patients with HFpEF are the natriuretic peptides: B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP).(8-9)

Circulating levels of these proteins are elevated in patients with HFpEF as compared to subjects without HF, but are lower than levels seen in patients with HFrEF. In patients with HFpEF, increased BNP is directly related to increased left ventricular (LV) diastolic filling pressure and end diastolic wall stress.(10) Because HFpEF patients have a smaller LV cavity and thicker LV walls, their end diastolic wall stress is much lower than in HFrEF, even in the setting of high diastolic pressures, thus, producing a lower stimulus for BNP production. In addition, other factors, independent of left ventricle diastolic pressure (LVDP) and diastolic stress also affect BNP levels in HFpEF patients. For any given LVDP in HFpEF patients, BNP levels are lower in obese patients and higher in women, older

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patients, and patients with concomitant pulmonary disease (chronic obstructive disease, pulmonary hypertension, pulmonary embolus) and renal dysfunction. In addition, studies using implantable hemodynamic monitors (IHM) in patients with HFpEF have demonstrated that LVDP is increased even when HFpEF patients are considered compensate.(11)

Like LVDP, BNP and NT-proBNP have become critical components of the diagnostic criteria for HFpEF proposed in HF guidelines.(12)

Van Veldhuisen et al. (5) examined the impact of LVEF on the prognostic merits of BNP in the COACH (Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure). The investigators found BNP levels were lower in HFpEF, but for a given BNP concentration, prognosis of those with HFpEF in COACH was just as poor as those with HFrEF, so a high BNP in a patient with HFpEF imparted similar prognostic information as it would in someone with HFrEF.(8)

The investigators rightfully consider how the results of this and the other studies showing prognostic merit of BNP or NT-proBNP in HFpEF might be harnessed for the betterment of patient care. This is of great importance, as we sadly do not yet have therapies that clearly benefit those with the clinical diagnosis of HFpEF. This may be because HF itself is a syndrome, not a specific diagnosis, and patients with HFpEF are a mixed bag of clinical and risk phenotypes, vastly more heterogeneous than are those with HFrEF.(13)

Trial PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) trial, only those HFpEF patients with elevated NT-proBNP concentrations showed potential benefit from allocation to angiotensin-converting enzyme inhibition.(13) On the other hand, Anand et al. (7) reported that among those treated in the I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction) study, only those with lower BNP values demonstrated benefit from angiotensin receptor blockade.(13)

In both trials, however, natriuretic peptides strongly predicted risk.(13)

It is hard to reconcile these divergent findings and it is very clearly, more data are needed to define this syndrome and the approach will be much more complex than using a single biomarker such as BNP to clarify care. To this extent, it is most likely to individually phenotype patients with HFpEF will involve a spectrum of tools, including clinical variables, blood testing, imaging, and hemodynamic factors, all integrated to inform specific aspects about the individual, and lead to better care.(13)

Biomarkers are only part of the spectrum of exams that contribute to the understanding of this pathology.

Markers of Extracellular Matrix Turnover

The myocardial extracellular matrix (ECM) plays a critical role in cardiac architecture and function.(14) The ECM is made of several components, including collagen. Collagen types I and III constitute the majority of the myocardial collagen. ECM balance is regulated by complex interactions between metalloproteinases (MMPs), which degrade collagen and other ECM components, and specific tissue inhibitors of MMPs (TIMPs).(14) Furthermore, the normal balance of collagen synthesis and degradation is altered by several factors, including LV pressures, myocardial ischemia and neurohormonal activation.(15-16) Cardiac collagen accumulation as a consequence of dysregulated collagen turnover may be an important mechanism for the progressive abnormalities of diastolic function that characterize HF-PEF.(17-18) Thus, measurement of circulating levels of biomarkers of collagen synthesis (e.g. procollagen type I carboxy terminal peptide (PICP) and procollagen type III amino-terminal propeptide (PIIINP)).(19,20,21) and degradation (e.g. carboxy-terminal telopeptide of collagen type I (CITP)).(22,23,24) MMPs and TIMPs may be a method for quantitating collagen turnover in HF-PEF, with implications for assessing disease severity, prognosis, and response to treatment.

Many small studies have demonstrated higher concentrations of PICP, PIIINP, and CITP in patients with HF-PEF compared to controls. Concentrations of these biomarkers were correlated with the degree of diastolic dysfunction, supporting the concept that increases in collagen synthesis and turnover contribute to the development of HF-PEF.(19,20) Regarding the prognostic value of ECM biomarkers in HFPEF,data are extremely limited and will require investigation in larger populations.

In a substudy of I-PRESERVE (n =334) (25), baseline levels of PIIINP were associated with the risk of all-cause mortality, as well as of HF death or hospitalization on univariate analysis.

Study of the RALES trial, which investigated the impact of spironolactone in patients with severe HF-REF, patients with higher concentrations of PIIINP appeared to derive the greatest benefit from spironolactone. These results suggest that PIIINP levels could potentially be integrated in the application of personalized research for the use of mineraloreceptor antagonists in HF.(26)

Galectin-3

Beyond markers of collagen turnover, other biomarkers may be relevant to the biology of myocardial fibrosis and progression of HFEFp. Galectin-3 is a 31 kD lectin binds to beta-galactosidase that is involved in numerous pathological processes, including inflammation, tumour growth and fibrosis. Increased Galectin-3 expression induces cardiac fibroblasts to proliferate and deposit type I collagen contributing to cardiac fibrosis and adverse remodelling.(27) Accordingly, levels of galectin- 3 anticipate the development of HF (28) and are increased in proportion to disease severity in patients with established HF. Recent data suggests that aldosterone induced vascular fibrosis may be mediated in part through galectin-3 suggesting its potential as a therapeutic target.(29) Amongst patients with HFEFr levels of galectin-3 appear to correlate with the risk for cardiovascular events, but may not add prognostic value to established markers such as natriuretic peptides.(30) However, in a cohort of 592 patients recently hospitalized for HF, galectin-3 levels did appear to provide incremental information regarding prognosis for the population with HFEFp (more so than in HFEFr), suggesting particular relevance of this biomarker in this population.(31)

Markers of Renal Function

Chronic Kidney Disease (CKD) is common in patients with HF and is an independent risk factor for cardiovascular morbidity and mortality.(32-33) The level of kidney function is commonly assessed by measurement of serum creatinine and estimated glomerular filtration rate (eGFR) (in ml/min/1.73 m2), but other markers such as cystatin C and urine protein may provide incremental information regarding CKD severity and prognosis. Even moderate degrees of renal dysfunction independently predict mortality in HF, whether EF is reduced or preserved.(32,34,35)

Cystatin C and urinary protein levels, may provide prognostic information beyond eGFR in patients with HFEFp. Both of these markers were important correlates of the risk of developing HFEFp in the epidemiologic cohorts of the PREVEND study (36) and in the Cardiovascular Health Study.(37) In acutely decompensated HF, a study (38) showed that Cystatin C levels were elevated above the reference range in

both HFEFr and HFEFp.

In one observational study of 218 patients with HFEFp (39), cystatin C levels>2.06 mg/L were associated with higher incidence of all-cause mortality , and this renal biomarker outperformed others, including eGFR and creatinine, with regard to risk prediction.

In the CHARM trials urinary albumin to creatinine ratio (UACR) was measured to 2310 patients (40); nearly one-third of patients without diabetes or hypertension had microalbuminuria or macroalbuminuria, with similar prevalence noted in those with HFEFp and HFEFr. Elevated UACR was associated with increased risk of death from cardiovascular causes or frequent rehospitalisation with worsening heart failure, even after adjustment for other prognostic variables, including renal function, diabetes and hemoglobin A1c. Mechanisms leading to increased albumin excretion in HF may involve a combination of renal venous congestion and reduced renal blood flow.(40). Cystatin C and urinary protein or albumin levels could be used to anticipate the development of HF-PEF and performing better than the currently used markers, such as eGFR and creatinine.(41)

Cardiac Troponins

With current high-sensitivity assays, circulating cardiac troponins are increasingly detectable in patients with HFEFr in proportion to HF severity. In the Valsartan in Heart Failure Trial (Val-HeFT), 10.4 % of subjects had detectable troponin T with a fourth generation clinical assay (detection limit 0.01 ng/mL); however, this proportion increased to 92 % when a high-sensitivity assay (detection limit 0.001 ng/mL) was used.(42) Although the pathophysiology of troponin release in HF remains uncertain, several factors, including subendocardial ischemia and myocyte necrosis, cardiomyocyte damage from inflammatory cytokines or oxidative stress, apoptosis, and leakage of troponin from the cytosolic pool due to increased membrane permeability, have been invoked.(43) Whatever the mechanism, the degree of troponin elevation appears to be a powerful predictor of mortality and cardiovascular events in both ambulatory and acutely decompensated patients with chronic HFEFr, even after adjustment traditional biomarkers including natriuretic peptides.(42,44,45) Limited data are available regarding the prognostic significance of troponin T elevations in the ambulatory population with HFEFp, though levels do appear to be elevated to an extent comparable to that seen in HFEFr.(46)

ST2

ST2 is a trans-membrane receptor belonging to the IL-1 receptor family that regulates inflammation and immunity.(41) The receptor has two isoform: a transmembrane bound form and a soluble circulating form sST2, wich lacks the intracellular and transmembrane. The soluble unbound isoform binds and removes IL-33 from the circulation, thus potentially promoting adverse remodeling and fibrosis. sST2 is a secreted decoy receptor that disrupts the binding of IL-33 with the full-length ST2 receptor, promoting cardiac hypertrophy, fibrosis, and ventricular dysfunction (41). In both patients postmyocardial infarction (41) and those with HF and reduced EF (41), serum levels of soluble ST2 are independently associated with mortality and disease progression and provide incremental prognostic value over NT-proBNP.(41) Limited data is available regarding the prognostic importance of soluble ST2 in the population with HFEFp. Amongst patients with acute decompensated HF, levels of ST2 appear to be lower in those with HFEFp than HFEFr, but are similarly associated with the risk of mortality at 1 year even after adjustment for natriuretic peptide levels (41) and ST2 may be a particularly relevant marker of disease progression.

GDF-15

Growth differentiation factor 15 (GDF-15) is a protein a member of the transforming growth factor-β cytokine superfamily, is increased in response to inflammation, pressure overload chronic and tissue injury, much like levels of natriuretic peptides.(41) Dates suggests that GDF-15 is a powerful marker of cardiometabolic risk in patients with stable and unstable coronary artery disease.(41) Increased circulating levels of GDF-15 are associated with an increased risk of developing HF in apparently healthy elderly individuals from the community.(41) In a cohort of 455 patients with chronic HFEFr, levels of GDF-15 were elevated in relationship to disease severity as measured by NYHA functional class and NT-proBNP levels, and were independently associated with prognosis.(41) Levels of GDF-15 appear to rise with time in chronic HFEFr and are not attenuated by treatment with Valsartan.(41) Increased levels of GDF-15 in association with age, diabetes, and CKD, as well as differences in GDF-15 and BNP in patients with HFEFr compared to HFEFp, suggest that GDF-15 may have a particular importance in diagnosis and prognostic for HFEFp.(46)

MicroRNAs

In addition to protein and peptide biomarkers, a number of plasma microRNAs (miRs) were examined in these patient groups; miRs are products of non-coding genes that act to repress protein translation. These miRs have been associated with inhibition of myocardial fibrosis and have not yet been applied as diagnostic or prognostic biomarkers in patients with HFEFp.(7)

Conclusions:

Biomarkers have helped improve current knowledge of pathophysiological mechanisms involved in HF-PEF and increasing data developing to support the role of selected markers for risk prediction in this population. Of the biomarkers available for routine clinical use, natriuretic peptides are the most extensively studied, and may facilitate both diagnosis and risk stratification in the population with HF-PEF. Markers of renal function including eGFR, Cystatin C and urinary protein provide incremental information regarding risk, and may identify a contribution of CKD to HF progression in those with preserved EF. Emerging markers of collagen turnover (particularly PIIINP and CITP), fibrosis (galectin-3), inflammation (GDF-15), cardiomyocyte stress (ST2), and damage (troponins) may provide incremental information about the specific pathophysiologic factors contributing to disease progression. Remains to be determined if these additional biomarkers in isolation or in combination with established markers such as natriuretic peptides is shows the benefit cost-effective or provides guidance regarding specific treatments for HF-PEF. Perhaps with additional study, measurement of these and other novel biomarkers may help to further refine clinical diagnosis and more effective therapy.(41)

REFERENCES

1. Braunwald E. Biomarkers in heart failure. The New England Journal of Medicine. 2008;358:2148-2159.
2. Senni M, Redfield MM. Heart failure with preserved systolic function. A different natural history? J Am Coll Cardiol. 2001;38:1277–82.
3. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation. 2011;123:2006-13,14.
4. De Keulenaer GW, Brutsaert DL. Systolic and diastolic heart failure are overlapping phenotypes within the heart failure spectrum. Circulation. 2011;123:1996-2004. discussion 5.

5. Kovacs SJ, Meisner JS, Yellin EL. Modelling of diastole (published correction appears in Cardiol Clin 2000;18:following table of contents). Cardiol Clin 2000;18:459-87.
6. Ahmed A, Nanda NC, Weaver MT, Allman RM, DeLong JF. Clinical correlates of isolated left ventricular diastolic dysfunction among hospitalized older heart failure patients. Am J Geriatr Cardiol. 2003;12:82-9.
7. Michael R. Zile, Catalin F. Baicu. Biomarkers of Diastolic Dysfunction and Myocardial Fibrosis: Application to Heart Failure with a Preserved Ejection Fraction J. of Cardiovasc Trans Res. 2013;6:501-515.
8. Van Veldhuisen DJ, Linssen GC, Jaarsma T, Van Gilst WH, Hoes AW, Tijssen JG, et al. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. Journal of the American College of Cardiology. 2013;61:1498-1506.
9. Jhund PS, Anand IS, Komajda M, McKelvie RS, Zile MR, Massie B, Carson PE, McMurray JJV. Change in N-terminal pro-B-type natriuretic peptide levels and outcomes in heart failure with preserved ejection fraction: an analysis of the I-PRESERVE study. Eur Heart J (in press); 2013.
10. Iwanaga Y, Nishi I, Furuichi S, Noguchi T, Sase K, Kihara, Y, et al. B-type natriuretic peptide strongly reflects diastolic wall stress in patients with chronic heart failure: comparison between systolic and diastolic heart failure. Journal of the American College of Cardiology. 2006;47(4):742-748.
11. Zile MR, Bennett TD, St. John Sutton M, Cho YK, Adamson PB, Aaron MF, et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiologic insights obtained from continuous monitoring of intracardiac pressures. Circulation. 2008;118(14):1433-1441.
12. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2012;33:1787-1847.
13. Januzzi JL. Natriuretic Peptides, Ejection Fraction, and Prognosis Parsing the Phenotypes of Heart Failure Journal of the American College of Cardiology. 2013;61(14):1507-1509.
14. Jugdutt BI. Ventricular remodelling after infarction and the extracellular collagen matrix: when is enough? Circulation. 2003;108:1395-403.
15. Kuster GM, Kotlyar E, Rude MK, et al. Mineralocorticoid receptor inhibition ameliorates the transition to myocardial failure and decreases oxidative stress and inflammation in mice with chronic pressure overload. Circulation. 2005;111:420-7.
16. Robert V, Silvestre JS, Charlemagne D, et al. Biological determinants of aldosterone-induced cardiac fibrosis in rats. Hypertension. 1995;26:971-8.
17. Lopez B, Gonzalez A, Diez J. Circulating biomarkers of collagen metabolism in cardiac diseases. Circulation. 2010;121:1645-54.
18. Querejeta R, Varo N, Lopez B, et al. Serum carboxy-terminal propeptide of procollagen type I is a marker of myocardial fibrosis in hypertensive heart disease. Circulation. 2000;101:1729-35.
19. Gonzalez A, Lopez B, Querejeta R, Zubillaga E, Echeverria T, Diez J. Filling pressures and collagen metabolism in hypertensive patients with heart failure and normal ejection fraction. Hypertension. 2010;55:1418-24.
20. Zile MR, Desantis SM, Baicu CF, et al. Plasma biomarkers that reflect determinants of matrix composition identify the presence of left ventricular hypertrophy and diastolic heart failure. Circ Heart Fail. 2011;4:246-256.
21. Martos R, Baugh J, Ledwidge M, et al. Diastolic heart failure: evidence of increased myocardial collagen turnover linked to diastolic dysfunction. Circulation. 2007;115:888-95.
22. Querejeta R, Lopez B, Gonzalez A, et al. Increased collagen type I synthesis in patients with heart failure of hypertensive origin: relation to myocardial fibrosis. Circulation. 2004;110:1263-8.
23. Barasch E, Gottdiener JS, Aurigemma G, et al. Association between elevated fibrosis markers and heart failure in the elderly: the cardiovascular health study. Circ Heart Fail. 2009;2:303-10.
24. Lopez B, Gonzalez A, Querejeta R, Larman M, Diez J. Alterations in the pattern of collagen deposition may contribute to the deterioration of systolic function in hypertensive patients with heart failure. J Am Coll Cardiol. 2006;48:89-96.
25. Krum H, Elsik M, Schneider HG, et al. Relation of peripheral collagen markers to death and hospitalization in patients with heart failure and preserved ejection fraction: results of the I-PRESERVE collagen substudy. Circ Heart Fail. 2011;4:561-8.
26. Zannad F, Alla F, Dousset B, Perez A, Pitt B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the randomized aldactone evaluation study (RALES). Rales Investigators. Circulation. 2000;102:2700-6.
27. McCullough PA, Olobatoke A, Vanhecke TE. Galectin-3: a novel blood test for the evaluation and management of patients with heart failure. Rev Cardiovasc Med. 2011;12:200-10.
28. Ho JE, Liu C, LyassA, et al.Galectin-3, a marker of cardiac fibrosis, predicts incident heart failure in the community. J Am Coll Cardiol. 2012;60:1249-56.
29. Calvier L, Miana M, Reboul P, et al. Galectin-3 mediates aldosterone-induced vascular fibrosis. Arterioscler Thromb Vasc Biol. 2013;33:67-75.
30. Felker GM, Fiuzat M, Shaw LK, et al. Galectin-3 in ambulatory patients with heart failure: results from the HF-ACTION study. Circ Heart Fail. 2012;5:72-8.
31. de Boer RA, Lok DJ, 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.
32. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol. 2001;38:955-62.
33. Jones RC, Francis GS, Lauer MS. Predictors of mortality in patients with heart failure and preserved systolic function in the Digitalis Investigation Group trial. J Am Coll Cardiol. 2004;44:1025-9.
34. Hillege HL, Nitsch D, Pfeffer MA, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation. 2006;113:671-8.
35. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol. 2000;35:681-9.

36. Brouwers FP, de Boer RA, van der Harst P, et al. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. Eur Heart J. 2013;34:1424-31.
37. Moran A, Katz R, Smith NL, et al. Cystatin C concentration as a predictor of systolic and diastolic heart failure. J Card Fail. 2008;14:19-26.
38. Bishu K, Deswal A, Chen HH, et al. Biomarkers in acutely decompensated heart failure with preserved or reduced ejection fraction. Am Heart J. 2012;164:763-70 e3.
39. Carrasco-Sanchez FJ, Galisteo-Almeda L, Paez-Rubio I, et al. Prognostic value of cystatin C on admission in heart failure with preserved ejection fraction. J Card Fail. 2011;17:31-8.
40. Jackson CE, Solomon SD, Gerstein HC, et al. Albuminuria in chronic heart failure: prevalence and prognostic importance. Lancet. 2009;374:543-50.
41. O'Meara E, de Denus S, Rouleau JL, Desai A. Circulating Biomarkers in Patients with Heart Failure and Preserved Ejection Fraction. Curr Heart Fail Rep. 2013;10:350-358.
42. Latini R, Masson S, Anand IS, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation. 2007;116:1242-9.
43. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker GM. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. J Am Coll Cardiol. 2010;56:1071-8.
44. Pascual-Figal DA,Manzano-Fernandez S, BoronatM, 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.
45. Masson S, Anand I, Favero C, et al. Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: data from 2 large randomized clinical trials. Circulation. 2012;125:280-8.
46. Santhanakrishnan R, Chong JP, Ng TP, et al. Growth differentiation factor 15, ST2, high-sensitivity troponin T, and N-terminal pro brain natriuretic peptide in heart failure with preserved vs. reduced ejection fraction. Eur J Heart Fail. 2012;14:1338-47.