Internal Medicine: Open Access

Berezin, Intern Med 2017, 7:2
DOI: 10.4172/2165-8048.1000236

Short Communication Open Access

Novel Biomarkers in Prediction of Heart Failure Related Outcomes: From Bench to Bedside

Berezin AE[1,2*]

[1]*Vita-Center, Zaporozhye, Ukraine*

[2]*Senior Consultant of Therapeutic Unit, Internal Medicine Department, State Medical University of Zaporozhye, Ukraine*

[*]**Corresponding author:** Berezin AE, Vita-Center, Zaporozhye and Senior Consultant of Therapeutic Unit, Internal Medicine Department, State Medical University of Zaporozhye, Ukraine. Tel: +380612894585; E-mail: dr_berezin@mail.ru

Received date: March 21, 2017; **Accepted date:** April 06, 2017; **Published date:** April 13, 2017

Abstract

Heart failure (HF) remains a global burden for patients with established cardiovascular (CV) disease. It has been postulated that underlying mechanisms of nature evolution of HF might be identified by measurement of some biomarker reflected various pathophysiological stages of cardiac dysfunction. In this way, cardiac biomarkers affected biomechanical stress, cardiac injury, fluid overload, inflammatory reaction, may be useful for prediction of development, progression, and prognosis of HF. The short communication is depicted to discussion around perspectives to use in routine HF clinical practice new biomarkers, i.e. procalcitonin, copeptin, heart-type fatty acid-binding protein; growth differentiation factor 15. It has concluded that these biomarkers are needed to be investigated in details, while there is suggestion that multiple biomarker models would be better in prediction HF evolution and outcomes than even single brand new biomarker.

Keywords: Chronic heart failure; Biomarkers; Procalcitonin; Copeptin; Heart-type fatty acid-binding protein; Growth differentiation factor 15; Prediction

Abbreviations EPCS: Endothelial Progenitor Cells; MPs: Circulating Microparticles; HF: Heart Failure: hFABP: Heart Type Of Fatty Acid-Binding Protein; Gal-3: Galectin-3; GDF-15: Growth Differentiation Factor-15; GFR: Glomerular Filtration Rate; FGF-15: Fibroblast Growth Factor-15; IL: Interleukin; NPs: Natriuretic Peptides: hs-CRP: Highly Sensitive C-Reactive Proteins: MMPs: Matrix Metalloproteinase; NGAL: Neutrophil Gelatinase Lipocaline; OPN: Osteopontin: OPG: Osteoprotegerin; TNF: Tumor Necrosis Factor.

Short Communication

Heart failure (HF) remains a leading cause of premature death in patients with established cardiovascular (CV) disease [1]. Prevalence of HF has been exhibiting a strong tendency to growth worldwide. Although there are several clinical guidelines regarding diagnosis, prevention and treatment of HF, prediction of HF development in various patient populations is still under scientific discussion. Biological markers have become a powerful tool for stratification HF patients at risk and biomarker-guided therapy [2]. Figure is reported the possible approaches regarding biomarker use in diagnostic and management of HF (Figure 1).

Updated clinical recommendations have been reported that the natriuretic peptides (NPs), galectin-3, high-sensitivity troponin and soluble ST2 protein are commonly used biomarkers, which remain a central part of routine clinical practice to stratify patients at risk of HF development, risk of primary admission/readmission to the hospital, and CV death [2]. Indeed, NPs are useful diagnostic and prognostic biomarkers in HF, particularly in patients with HF with reduced left ventricular ejection fraction. Galectin-3, which indicates cardiac fibrosis and inflammation, is a documented biomarker of prognosis in HF and indicator of a risk of HF development in general population. The high-sensitive cardiac troponin T is a sensitive biomarker of myocardial damage and predictor of acute decompensated HF. Soluble ST2 (suppression of tumorigenity) is a receptor for the interleukin-33-a member of the IL-1 family of cytokines. Recent clinical studies have exhibited an association between circulating ST2 level and coronary artery disease, cardiac dysfunction, all-causes mortality and CV mortality [3,4].

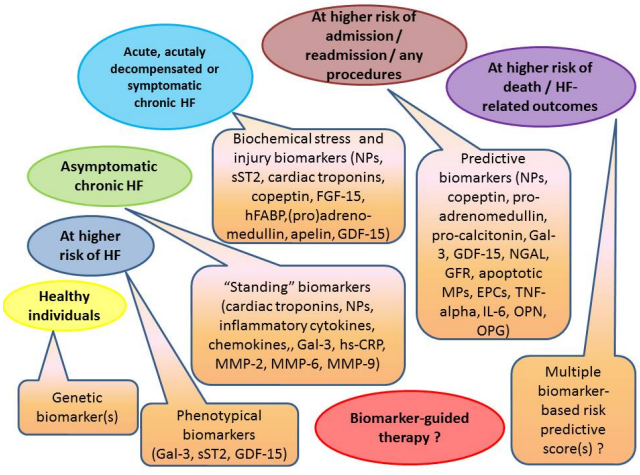

Figure 1: The biomarker use in diagnostic and management of HF.

Confusingly, their role in modification of treatment care considerably relates to aging, CV and metabolic co-morbidities, kidney clearance, and higher individual biological variability of biomarkers, which negatively effects on interpretation of circulating biomarkers' level [5]. Moreover, all conventional biomarkers have limited clinical

value for identifying future risk of adverse outcomes in HF [6]. In this context, novel biomarkers are required to assist in the titration of medical therapy and improve prediction of widely used scores [7].

Procalcitonin, copeptin, heart-type fatty acid-binding protein (hFABP) and growth differentiation factor 15 (GDF-15) has been suggested to be novel biomarkers in HF.

Procalcitonin is known a precursor of the calcitonin, which is produced and actively secreted by the parafollicular C cells of the thyroid gland and involved in regulation of calcium homeostasis [8]. Recent clinical studies have shown that procalcitonin as an inflammatory biomarker had a pretty accurate diagnostic ability to sepsis, shock, bacterial complications of some diseases [9-11]. Additionally, this biomarker may help to manage the patients with HF when antibiotic use is needed or their critical state has been verified [7]. However, there is not strong evidence regarding procalcitotin use in biomarker-guided therapy to adjust dosage of drugs for HF individuals.

Copeptin is C-terminal peptide derived from the precursor molecule of arginine vasopressin, which plays a pivotal role in fluid retention and electrolyte homeostasis [12]. In the general population elevated level of copeptin strongly associated with increased CV mortality [13]. Additionally, based on results of serial measurements of copeptin level it has been suggested that the increased copeptin concentration or trend to elevation of one are an independent risk factor for long-term HF-related clinical outcomes and sudden death in patients with established CV disease [14-16]. Being able to better predict all-cause mortality and HF-related risks including death and admission to the hospital copeptin might be considered as much more accurate biomarker than natriuretic peptides for optimize medical care in HF patients [17,18]. Unfortunately, there are large body of evidence regarding that the level of copeptin might relate closely to some metabolic abnormalities including hyperglycemia that sufficiently limits the predictive power of the biomarker in serial measurements especially in patients with diabetes and obesity [17,19]. However, the improvement of diagnostic reliability of copeptin may achieve by means use of combined biomarker strategy, in particular it might be based on copeptin and natriuretic peptides (N-terminal pro-brain natriuretic peptide, mid-regional pro-atrial natriuretic peptide) [20,21]. Finally, circulating level of copeptin is now recognized a promising biomarker with better discriminative value for both all-cause mortality and HF-related outcomes general population and individuals with established CV disease.

The main biological role of heart type of FABP (hFABP) is to facilitate the long-chain fatty acids re-uptake, attenuate calcium transport in cardiomyocytes and regulate inflammatory response in reply to some lipid signals [22]. hFABP is predominantly expressed in cardiomyocytes and is powerful biomarker of myocardial injury. Recent studies have shown that the hFABP has better predicted CV outcomes to other biomarkers of cardiac damage, i.e. myoglobin and high-sensitive cardiac troponins [5,17,23], whereas elevated intestinal FABP would identify patients with advanced HF who have severe fluid retention and intestinal congestion [24]. Overall, the hFABP may better provide prognostic information on survival and more precise reflect a risk of major CV events during hospitalization period and short-time after discharge than natriuretic peptides, cardiac troponins and galectin-3. However, the role of several types of FABP in HF is not fully clear. Large clinical studies are required to more accurately explain the predictive value of these biomarkers.

Growth differentiation factor (GDF)-15 belongs to the superfamily of transforming growth factor-β [25]. GDF-15 is widely expressed on the surfaces of various cells. In HF GDF-15 is secreted by injured cardiomyocytes in response to ischemia, reperfusion, inflammatory cytokine stimulation and exposure to biomechanical stress [17]. Elevated level of circulating GDF-15 was found in HF individuals irrespectively etiology of cardiac dysfunction [26]. There is strong evidence regarding being tight interrelationship between circulating level of GDF-15 and HF signs and symptoms, reduced left ventricular ejection fraction [27]. Although serial biomarker evaluation has not showed superiority of incremental predictive ability in GDF-15 versus natriuretic peptides in acute HF [28], in chronic HF multiple marker strategy based on GDF-15, galectin-3 and natriuretic peptides might exhibit several advantages before conventional approach in ability to predict all-cause mortality, CV mortality and HF-related outcomes in outpatients with HF [29,30].

Finally, there are several controversies regarding importance of predictive value for survival and incremental prognostication in diagnosis of HF. There is need in larger clinical studies with higher statistical power and head-to-head comparison of biomarkers to clear their role in diagnosis and guided therapy of HF.

Conclusion

Although recent clinical trials have been exhibited much more information regarding biomarker use in prognostication of HF, there is considerable limitation in head-to-head comparison of several biomarkers and biomarker-based strategy to treat of HF. All these are a cause of some speculations around advantages and shortcomings of biomarker-based management of HF including new biological indicators, such as procalcitonin, copeptin, hFABP and GDF-15. Novel biomarkers are needed to be investigated in details, while there is suggestion that multiple biomarker models would be better in prediction HF evolution and outcomes than even single brand new biomarker.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, et al. (2016) Authors/Task Force Members. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 37: 2129-2200.
2. Wettersten N, Maisel AS (2016) Biomarkers for heart failure: An update for practitioners of internal medicine. Am J Med 129: 560-567.
3. Ciccone MM, Cortese F, Gesualdo M, Riccardi R, Di Nunzio D, et al. (2013) A novel cardiac bio-marker ST2: A review. Molecules 18: 15314-15328.
4. Marzullo A, Ambrosi F, Inchingolo M, Manca F, Devito F, et al. (2016) ST2L transmembrane receptor expression: An immunochemical study on endarterectomy samples. PLoS One 11: e0156315.
5. Berezin AE (2016) Prognostication in different heart failure phenotypes: the role of circulating biomarkers. Journal of circulating biomarkers 5: 01.
6. Nymo SH, Aukrust P, Kjekshus J, McMurray JJ, Cleland JG, et al (2017) Limited added value of circulating inflammatory biomarkers in chronic heart failure. JACC Heart Fail 5: 256-264.
7. Pouleur AC (2015) Which biomarkers do clinicians need for diagnosis and management of heart failure with reduced ejection fraction? Clin Chim Acta 443: 9-16.

8. Ryu JA, Yang JH, Lee D, Park CM, Suh GY, et al. (2015) Clinical usefulness of procalcitonin and c-reactive protein as outcome predictors in critically ill patients with severe sepsis and septic shock. PLoS One 10: e0138150.
9. Reiner MM, Khoury WE, Canales MB, Chmielewski RA, Patel K, et al. (2017) Procalcitonin as a biomarker for predicting amputation level in lower extremity infections. J Foot Ankle Surg. S1067-S2516.
10. Hayashida K, Kondo Y, Hara Y, Aihara M, Yamakawa K (2017) Head-to-head comparison of procalcitonin and presepsin for the diagnosis of sepsis in critically ill adult patients: a protocol for a systematic review and meta-analysis. BMJ Open 7: e014305.
11. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J (2004) Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: A systematic review and meta-analysis. Clin Infect Dis 39: 206-217.
12. Morgenthaler NG, Struck J, Alonso C, Bergmann A (2006) Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clin Chem 52: 112-119.
13. Remde H, Dietz A, Emeny R, Riester A, Peters A, et al. (2016) The cardiovascular markers copeptin and high-sensitive C-reactive protein decrease following specific therapy for primary aldosteronism. J Hypertens 34: 2066-2073.
14. Moayedi Y, Ross HJ (2017) Advances in heart failure: a review of biomarkers, emerging pharmacological therapies, durable mechanical support and telemonitoring. Clin Sci (Lond) 131: 553-566.
15. Krane V, Genser B, Kleber ME, Drechsler C, März W, et al. (2017) Copeptin associates with cause-specific mortality in patients with impaired renal function: results from the LURIC and the 4D study. Clin Chem.
16. Yan JJ, Lu Y, Kuai ZP, Yong YH (2017) Predictive value of plasma copeptin level for the risk and mortality of heart failure: A meta-analysis. J Cell Mol Med.
17. Berezin AE (2015) Biological markers of cardiovascular diseases. Part 4. Diagnostic and prognostic value of biological markers at risk stratification among patients with heart failure. LAMBERT Academic Publishing GmbH, pp: 329.
18. Savic-Radojevic A, Pljesa-Ercegovac M, Matic M, Simic D, Radovanovic S, et al. (2017) Novel biomarkers of heart failure. Adv Clin Chem 79: 93-152.
19. Smaradottir MI, Ritsinger V, Gyberg V, Norhammar A, Näsman P, et al. (2017) Copeptin in patients with acute myocardial infarction and newly detected glucose abnormalities - A marker of increased stress susceptibility? A report from the Glucose in Acute Myocardial Infarction cohort. Diab Vasc Dis Res 14: 69-76.
20. Sahin I, Gungor B, Ozkaynak B, Uzun F, Küçük SH, et al. (2017) Higher copeptin levels are associated with worse outcome in patients with hypertrophic cardiomyopathy. Clin Cardiol 40: 32-37.
21. Herrero-Puente P, Prieto-García B, García-García M, Jacob J, Martín-Sánchez FJ, et al. Predictive capacity of a multimarker strategy to determine short-term mortality in patients attending a hospital emergency Department for acute heart failure. BIO-EAHFE study. Clin Chim Acta. 2017; 466: 22-30.
22. Chmurzynska A (2006) The multigene family of fatty acidbinding proteins (FABPs): Function, structure, and polymorphism. J Appl Genet 47: 39-48.
23. Qian HY, Huang J, Yang YJ, Yang YM, Li ZZ, et al. (2016) Heart-type fatty acid binding protein in the assessment of acute pulmonary embolism. Am J Med Sci 352: 557-562.
24. Kitai T, Kim YH, Kiefer K, Morales R, Borowski AG, et al. (2017) Circulating intestinal fatty acid-binding protein (I-FABP) levels in acute decompensated heart failure. Clin Biochem pii: S0009-9120(17)30011-5.
25. Kempf T, Wollert KC (2009) Growth differentiation factor-15: A new biomarker in cardiovascular disease. Herz 34: 594-599.
26. Chan MM, Santhanakrishnan R, Chong JP, Chen Z, Tai BC, et al. (2016) Growth differentiation factor 15 in heart failure with preserved vs. reduced ejection fraction. Eur J Heart Fail 18: 81-88.
27. Hage C, Michaëlsson E, Linde C, Donal E, Daubert JC, et al. (2017) Inflammatory Biomarkers Predict Heart Failure Severity and Prognosis in Patients With Heart Failure With Preserved Ejection Fraction: A Holistic Proteomic Approach. Circ Cardiovasc Genet 10: e001633.
28. Demissei BG, Cotter G, Prescott MF, Felker GM, Filippatos G, et al. (2017) A multimarker multi-time point-based risk stratification strategy in acute heart failure: results from the RELAX-AHF trial. Eur J Heart Fail.
29. Berezin AE, Kremzer AA, Martovitskaya YV, Samura TA, Berezina TA, et al. (2015) The utility of biomarker risk prediction score in patients with chronic heart failure. Int J Clin Exp Med 8: 18255-18264.
30. Berezin AE (2015) The risk stratification in heart failure patients: The controversial role of high-sensitive ST2. J Integr Cardiol 1: 216-217.