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Growth-Differentiation Factor-15 as Additional Prognostic Biomarkers in Heart Failure

Berezin AE*

Internal Medicine Department, State Medical University of Zaporozhye, Zaporozhye, Ukraine

***Correspondence author:** Berezin AE, Professor, MD, PhD, Private Clinic "Vita-Center", Senior Consultant of Therapeutic Unit, Internal Medicine Department, State Medical University of Zaporozhye, 3, Sedova Str., Zaporozhye, Ukraine, Tel: +380612894585; E-mail: dr_berezin@mail.ru; aeberezin@gmail.com

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Abstract

Heart Failure (HF) remains to be a leading factor of cardiovascular morbidity and mortality. Although risk stratification of HF is promising prediction care, there are several controversies regarding choosing more optimal combinations of biomarkers and method (single versus serial measurements) of biomarker use in routine clinical practice. Growth differentiation factor-15 (GDF-15) is considered a biomarker associated with cardiac/vascular remodeling, oxidative stress, fibrosis and inflammation that were proposed to stratify HF patients at risk of death. It has been suggested that GDF-15 adding to natriuretic peptides or other conventional biomarkers (soluble ST2, cardiac troponins and galectin-3) might improve discriminative value of entire predictive models. The short communication is depicted the discussion about the perspectives of clinical use of GDF-15 in risk stratification of HF.

Keywords: Heart Failure (HF); Biomarkers; Growth differentiation factor-15; Prediction

Introduction

Heart Failure (HF) is reported as a leading cause of premature Cardiovascular (CV) death and increased hospitalization rate in patients with established CV disease [1,2]. Although frequency of newly diagnosed HF in developed countries exhibits a trend to decrease, there is evidence regarding steadily growth of HF patients' population worldwide [3]. Biological markers are widely used to stratify individuals at higher risk of HF and diagnose of asymptomatic and symptomatic cardiac dysfunction regardless its etiology [4,5]. Moreover, biomarker target therapy of HF is considered as promising strategy to improve clinical outcomes amongst HF patients, while its role is not still confirmed [6]. According to contemporary Scientific Statement from the American Heart Association regarding use of biomarkers in HF only Natriuretic Peptides (NPs), cardiac troponins, galectin-3 and soluble ST2 receptors (sST2) have validated to clinical targets mentioned above [6]. However, there is a large body of evidence regarding several limitations in biomarker approaches especially in predicting incident of CV events and CV mortality among asymptomatic individuals from the general population, beyond traditional CV risk factors including diabetes mellitus, kidney disease, age, as well as medication use and conventional echocardiographic/other images measures [7,8]. In this context, the discovery and validation of novel biomarkers or multiple biomarker strategy approaches that could improve predictive abilities of conventional biomarkers such as NPs in HF risk stratification appear to be fairly promising.

Growth differentiation factor-15 (GDF-15) is considered a biomarker associated with cardiac/vascular remodeling, oxidative stress, fibrosis and inflammation that were proposed to stratify HF patients at risk of death [9]. In physiological states GDF-15 is secreted by cardiac myocytes and it regulated growth and proliferation of tissues located in heart and vessels [10]. Therefore, GDF-15 is realized by cardiac cells due to fluid retention and pressure overload, as well as it produced in resulting in inflammation and cell-to-cell cooperation [11].

Recent clinical studies have shown that plasma levels of GDF-15 have sufficiently increased in acute myocardial infarction [12], diabetes mellitus [13], acute and chronic HF regardless its etiology [14,15], as well as independently predicted long-term all-cause mortality and CV events even after adjusting for age, gender, kidney clearance, traditional CV risk factors and other biomarkers, such as NPs, cardiac troponins, heart-type fatty acid-binding protein, sST2, high-sensitivity C-reactive protein and galectin-3 [9,16-19]. Interestingly, GDF-15 is able to enhance prognostication of NPs beyond traditional CV risk factor, and echocardiography parameters in individuals without known CV disease [12] and acute/chronic HF [20].

However, there are several controversies regarding the abilities of GDF-15 to improve prognostication of conventional biomarkers in HF. First controversy relates to the fact that maximizing discriminatory accuracy of repeat measurements of GDF-15 added to NPs in HF was superior to single measurement [21]. Second controversy associated with clinical evidence of advantages of individually adjusted multiple marker approaches in provision of the greatest prognostic improvement among patients with various HF phenotypes [22,23]. Although GDF-15 was useful to detect prevalent of any HF phenotype in addition to NPs, the discriminative value of NPs, GDF-15, sST2, galectin-3 and cardiac troponins in general population was similar [24,25]. Third controversy is follow: In obese and diabetes mellitus subjects GDF-15 was the best predictor for all-cause mortality to NPs, while discriminative value for both markers in combination was not better than single biomarker use [26]. Finally, there was no evidence that GDF-15 had sufficiently improved treatment options of HF in single and serial measures [27]. However, more large clinical studies require explaining the advantages of GDF-15 in multiple biomarker strategy in HF.

Conclusion

In conclusion, multiple biomarker strategies biased on NPs, sST2, cardiac troponins and probably GDF-15 are superior than single biomarker measure in prediction of HF, as well as serial measures versus single determination of only biomarker are superior to optimize HF patient management. However, individualized biomarker approaches remains to be fairly personally adjusted to be adequately assayed and prospectively assessed in long-term period. Although GDF-15 appears to be promising biomarker in HF risk stratification, its role in prognostication requires to be additionally confirmed in large clinical trials.

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