Cardiovascular (CV) diseases are the leading causes of mortality and disability in general population worldwide (1). Contemporary decision-making of both prevention and treatment of CV diseases bases on risk stratification and enroll the appropriate patients for further procedures and medical care (2,3). Because there is considerable heterogeneity in CV risk assessment with clinical tools and even when one more CV risk score systems are used, the exact CV risk determination might be facilitated by an implementation of individual CV risk stratification with biomarkers reflected numerous various faces of pathogenesis of the disease (4). Recent clinical trials have shown that N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponins, galectin-3, and soluble ST2 could be the best tool for cardiovascular (CV) risk stratification in general population as well as in individuals with CV diseases. However, abilities of these biomarkers to predict CV mortality rate are variable and depends on age, sex, kidney function and metabolic comorbidities. Growth-differentiation factor-15 (GDF-15) belongs to the transforming growth factor superfamily that regulates mitochondrial function of wide range of cells that involve in inflammation, oxidative stress, apoptosis, immune reaction, fibrosis, reparation and malignancy. This short commentary is depicted the possibilities to extrapolate the predictive capabilities of GDF-15 from metabolic and tumor diseases to CV diseases.

**Key Words:** Heart failure; Cardiovascular disease; Biomarkers; Growth-differentiation factor-15; Prognosis; Clinical outcomes; Predictive value

Growth differentiation factor 15 in cardiovascular diseases: Are we needed novel biomarker?

**Alexander Berezin**

**ABSTRACT**

Recent clinical trials have shown that biological markers presumably natriuretic peptides, galectin-3, soluble ST2 could be the best tool for cardiovascular (CV) risk stratification in general population as well as in individuals with CV diseases. However, abilities of these biomarkers to predict CV mortality rate are variable and depends on age, sex, kidney function and metabolic comorbidities. Growth-differentiation factor-15 (GDF-15) belongs to the transforming growth factor superfamily that regulates mitochondrial function of wide range of cells that involve in inflammation, oxidative stress, apoptosis, immune reaction, fibrosis, reparation and malignancy. This short commentary is depicted the possibilities to extrapolate the predictive capabilities of GDF-15 from metabolic and tumor diseases to CV diseases.

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systolic pressure, mean pulmonary artery pressure, pulmonary blood flow, systemic blood flow and pulmonary vascular resistance, and as well as a lower mixed venous oxygen saturation (16). It has been determined that the diagnostic value of NT-proBNP and GDF-15 in turn of pulmonary arterial hypertension was similar. In atherosclerosis GDF-15 appears an ability to prevent ischemia and necrosis of cardiac cells, while a concentration of it in peripheral blood correlates well with cardiac fibrosis.

**GROWTH-DIFFERENTIATION FACTOR-15 IN CV PREDICTION**

GDF-15 was defined as good prognosticator of CV complications in patients with diabetes mellitus (17). There is evidence received in the KAROLA study that elevated levels of GDF-15 predicted both 10-year CV mortality rate and all-cause mortality rate (9). In the JUVENTAS (Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-Arterial Supplementation) trial in patients with established peripheral artery disease elevated levels of GDF-15 were found a predictor of critical limb ischemia, increased risk of major amputation and all-cause mortality (18). Elevated GDF-15 associated with a lack of reverse remodeling and increased mortality after transcatheter aortic valve replacement procedure and improves risk prediction of CV mortality rate adding to traditional score model (19). It has found that are associated with an increased yearly rate of all-cause chronic obstructive pulmonary disease exacerbations in out-patients (20). Because GDF-15 was found as an independent biomarker of all-cause mortality, CV death and non-fatal CV events in patients with coronary artery disease and atherosclerosis, it could support prescreening and selection high risk patients with non-ST-elevation acute coronary syndrome for early revascularization and aggressive medical therapy. Additionally, GDF-15 is considered as promising prognostic biomarker that predicts poor survival in not just individuals with chronic diseases, but in patients with critically illness including acute heart failure, sepsis, multiple organ failure (21,22).

The HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) study was yielded that GDF-15 in plasma positively associated with severity of chronic heart failure (HF), peak concentration of NT-proBNP, all-cause death rate and inversely related to peak oxygen uptake on cardiopulmonary exercise testing (23). Interestingly, in the study the serum levels of GDF-15 in chronic HF patients with preserved left ventricular (LV) ejection fraction (EF) were similar to those in reduced LVEF (HFREF), while it associated with the severity of HF symptoms, echocardiographic parameters of LV dysfunction, 6 minute walk test distance and SF-36 physical score (23). However, in chronic HF with preserved LVEF (HFpEF) GDF-15 did not improve diagnostic discrimination when it is added to clinical status, cardiac pulmonary exercise testing findings, and traditional biomarkers including high sensitive troponin T, galectin-3, soluble ST2 and NT-proBNP (24). In contrast, in HFREF diagnostic accuracy of GDF-15 was not inferior as that of NT-proBNP and combining both biomarkers may improve diagnostic discrimination (25). Probably, multiple biomarkers including GDF-15 (i.e., high sensitive Creatinine protein + soluble ST2 + galectin-3 / NT-proBNP) added to novel score could predict HFpEF (26).

In conclusion, GDF-15 appears to be a promising biomarker for individual CV risk stratification, while this biomarker should be probably considered as a component of multiple biomarkers’ CV score for future implementation in the clinical practice. However, the role of GDF-15 requires to be investigated in large clinical trials with higher statistical power.

**REFERENCES**