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Review

Clinical and therapeutic implication of biomarkers in heart failure with preserved ejection fraction. Current approach and future perspectives

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Abstract. Heart failure with preserved ejection fraction (HFpEF) is a common clinical syndrome in 65 years old patients and represents 50% of all heart failure cases, with a 5 years survival of 35-40%, similar to or lower than malignancies. Nowadays it is becoming a public health problem by its increasing prevalence, leading cause of morbidity and mortality, challenging diagnosis, high hospitalization rates and costs, limited therapeutic options and poor quality of life of these patients. Defined as a complex and heterogeneous clinical syndrome, its phenotypic appearance depends on the underlying conditions: arterial hypertension, diabetes mellitus, metabolic syndrome, anemia, chronic kidney disease, chronic obstructive pulmonary disease, atrial fibrillation. These co-morbidities contribute to a systemic inflammatory syndrome, associate microvascular endothelial inflammation, cardiac fibrosis, mechanisms involved in the complex pathogenesis of HFpEF.The aim of our current review is to describe molecular biomarkers involved in HFpEF pathogenesis, myocardial fibrosis, heart remodeling, inflammation, biomarkers which might provide novel diagnostic and prognostic tools, cardio protection or therapeutic targets, as well as novel therapeutic strategies in HFpEF in order to improve therapy response, survival rates and quality of life of these patients.

Key Words: heart failure with preserved ejection fraction, biomarkers, diastolic dysfunction, diagnosis, prognosis, therapeutic target, life quality, cardio protection.

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is a common clinical syndrome in patients over 65 years old, having a 5 years survival of 35-40%, similar or lower than human malignancies.

HFpEF is becoming a public health problem by its increasing prevalence, its high morbidity, mortality and hospitalization rates, limited diagnostic tools, poor quality of life and high healthcare costs induced by frequent hospitalizations and reduced therapeutic options. HFpEF is a clinical syndrome, frequently diagnosed in elderly patients and more often in women, where patients have signs and symptoms of heart failure with a left ventricular ejection fraction (LVEF) ≥50%, HFpEF is a heterogeneous syndrome by its etiology and pathogenetic mechanisms (Ahmeti et al 2017; Alcaide-Aldeano et al 2020; AlHabeeb et al 2019; Brown et al 2017; Choi et al 2019; Cuijpers et al 2020; Dunlay et al 2017; Dzhioeva et al 2020; Franceschini et al 2018; Heinzel et al 2020; Honigberg et al 2020; Kalogirou et al 2020; Ma et al 2020; Michalska-Kasiczak et al 2018; Napier et al 2018; Plitt et al 2018; Schmitter et al 2014; Senthong et al 2017; Shah et al 2020; Tannenbaum et al 2015; Upadhya et al 2018; Upadhya & Kitzman 2017; Wintrich et al 2020).

HFpEF epidemiology

Heart failure has been defined as a global pandemic disorder affecting around 26 million people worldwide. HFpEF represents 50% of all heart failure cases and its prevalence is increasing in association with obesity pandemics, type 2 diabetes mellitus (T2DM), hypertension, coronary artery disease western lifestyle type, aging, ischemic heart disease (Brown et al 2017; Bui et al 2011; Cui et al 2020; Dunlay et al 2017; Kalogirou et al 2020; Kurmani et al 2017; Lam et al 2011; Michalska-Kasiczak et al 2018; Mishra et al 2021; Nair 2020; Pfeffer et al 2019; Plitt et al 2018; Roger 2013; Savarese et al 2017; Shah 2017b; Shear 2019; Suna et al 2020; Tannenbaum et al 2015; Upadhya & Kitzman 2017; Upadhya et al 2020).

HFpEF pathogenesis

HFpEF has a large phenotypic heterogeneity and presents diastolic dysfunction, cardiac remodeling (fibrosis, inflammation,

and hypertrophy) and is frequently associated with multiple comorbidities, which induce a chronic inflammatory syndrome and underlie HFpEF pathogenesis (Cuijpers et al 2020; D'Amario et al 2019; Dzhioeva et al 2020; Gevaert et al 2019; Heinzel et al 2020; Kao et al 2020; Liu et al 2020; Ma et al 2020; Michalska-Kasiczak et al 2018; Mishra et al 2021; Pfeffer et al 2019; Plitt et al 2018; Schmitter et al 2014; Shah 2017a; Shah et al 2020; Shear 2019; Simmonds et al 2020; Upadhya et al 2020; Wintrich et al 2020).

Complex cellular and molecular mechanisms are involved in HFpEF pathogenesis mainly triggering a pro inflammatory syndrome which alters endothelium physiology, then perivascular environment activate molecular pathways involved in myocardial fibrosis which is strongly correlated with diastolic dysfunction in HFpEF and increased levels of inflammatory biomarkers (IRL1, CRP, GDF15, TNF-α, sSt-2, pentraxin-3) (Bayes-Genis et al 2020; Bielecka-Dabrowa et al 2017; Cuijpers et al 2020; D'Amario et al 2019; de Boer et al 2019; Heinzel et al 2020; Kanagala et al 2015; Ma et al 2020; Mishra et al 2021; Pfeffer et al 2019; Schiattarella et al 2019; Schmitter et al 2014; Schulte et al 2015; Shah et al 2016; Simmonds et al 2020; Upadhya et al 2020; Watson et al 2021).

The aim of our current review is to describe molecular biomarkers involved in myocardial fibrosis, heart remodeling, inflammation in HFpEF and highlight their diagnostic, prognostic or therapeutic value in HFpEF. New cell and molecular biology, genomic acquisition (molecular biomarkers) may become useful biomarkers for positive diagnostic, prognosis and therapy response in HFpEF, but also important tools in developing precise therapeutic strategies in HFpEF in order to decrease hospitalization rates and improve quality of life of these patients.

Biomarkers in HFpEF

Functional or molecular biomarkers studied in HFpEF reflect the pathogenetic mechanisms involved in HFpEF, patient heterogeneity, HFpEF phenotypes and explain cardiac dysfunction, neurohormonal activation and are correlated with systemic inflammation, organ dysfunction and associated comorbidities, oxidative stress and various molecular alteration underlying HFpEF. Biomarkers correlated with functional tests in HFpEF are considered functional biomarkers and those identified by genetic or genomic tests are molecular biomarkers.

Troponins

Troponins (I and T) are proteins found in cardiomyocytes and released during acute myocardial injury. (Freitas et al 2020; Fudim et al 2018; Januzzi et al 2012; Katrukha et al 2021; Obokata et al 2018) Increased levels of troponins can be considered as predictive biomarkers of subclinical alterations of cardiac structures in cardiac remodeling processes and diastolic dysfunction in patients which will develop HFpEF, also might be considered prognostic biomarkers of adverse cardiac events in HFpEF patients (Freitas et al 2020; Myhre et al 2019; Obokata et al 2018; Suzuki et al 2019).

Troponins I and T high levels are associated with high mortality and hospitalization rates in patients diagnosed with HFpEF, Troponin I levels are correlated with worse cardiac structure, advanced LV hypertrophy and diastolic dysfunction and increased risk of adverse cardiac events in HFpEF patients, HF hospitalization and mortality rate (Freitas et al 2020; Fudim et al 2018; Gohar et al 2017; Myhre, O'Meara, et al 2018; Suzuki et al 2019; Thawabi et al 2017). Troponin levels in HFpEF are also correlated with LV filling pressures (Obokata et al 2018). Increased Troponin T levels are an indicator of cardiomyocyte injury associated with worse diastolic dysfunction, higher LVMI and increased risk of adverse cardiac events and poor prognosis in HFpEF patients (Myhre et al 2019; Obokata et al 2018; Suzuki et al 2019).

Natriuretic peptides (NP)

Natriuretic peptides (NP) explain heart failure pathogenesis, development and progression, but are also useful biomarkers for the diagnosis of diastolic dysfunction, HFpEF, acute or chronic heart failure patients, atrial fibrillation (AF) or coronary artery disease (CAD). MR-proANP and BNP are useful biomarkers for acute heart failure diagnostic in dyspneic patients, MR-proANP, BNP and NT-proBNP are prognostic biomarkers in patients diagnosed with with acute and chronic heart failure, while BNP and NT-proBNP are considered predictive biomarkers for mortality and cardiovascular events in asymptomatic patients. There are 3 endogenous natriuretic peptides secreted as pre-hormones: atrial natriuretic peptide (ANP), B type natriuretic peptide (BNP) and C type natriuretic peptide (CNP). Most studied and used NP in HFpEF positive diagnosis and prognosis of heart failure are brain natriuretic peptide (BNP) and the N-terminal pro-BNP (NT-proBNP). Recently described molecules, middle region pro atrial natriuretic peptide (MR proANP) have better specificity for HFpEF diagnosis. ANP are secreted by atria in response to atrial stress and LV hypertrophy, extracardiac sources of ANP are the hypothalamus, the thyroid and the lungs. ANP has three circulating forms: αANP, βANP and proANP (Abernethy et al 2018; Baba et al 2019; Moe 2006; Myhre, Vaduganathan, et al 2018; Schmitter et al 2014; Shah et al 2016; Tanase et al 2019; Volpe et al 2016).

The biologically active form of BNP is BNP32, mainly secreted by the ventricular myocardium as a response to myocardial stretch. BNP inhibits necrosis and fibrosis and exhibits anti- inflammatory effects. In HFpEF, NP levels BNP ≥35pg/mL and NT pro BNP ≥ 125pg /mL are considered diagnostic parameters if they are associated with at least one echocardiographic parameter: LAVI >34 mL/m2, LV hypertrophy LVMI≥115/95g/m2 or diastolic dysfunction (Kaplon-Cieslicka et al 2020; Pieske et al 2019, 2020; Remmelzwaal et al 2020).

With exception for its diagnostic and prognostic significance in HFpEF, NP levels using NP analogs or breakdown inhibition, might become a therapeutic target in HFpEF. Circulating levels of NP are increased in patients diagnosed with HFpEF in comparison with healthy subjects, but decreased in comparison with HFrEF patients (Baba et al 2019; Kanagala et al 2020; Moe 2006; Myhre, Vaduganathan, et al 2018; Palazzuoli et al 2013; Remmelzwaal et al 2020; Schmitter et al 2014; Shah 2017b; Shah et al 2020; Tanase et al 2019; Thomas et al 2006; Volpe et al 2016; Yamaguchi et al 2004; Zile et al 2013).

NP decreased plasma levels are correlated with other factors: ethnicity, age, sex, obesity, atrial fibrillation, insulin resistance, hepatic, pulmonary or kidney dysfunctions, nepresilin activity, increased androgen hormone levels and NPPA/ NPPB genetic polymorphisms (s5068, rs198358), explaining its low

specificity for HFpEF diagnostic. NTproBNP correlates with poor clinical outcome in HF patients (Baba et al 2019; Fu et al 2018; Kanagala et al 2020; Moe 2006; Myhre, Vaduganathan, et al 2018; Newton-Cheh et al 2009; Palazzuoli et al 2013; Remmelzwaal et al 2020; Salah et al 2019; Schmitter et al 2014; Shah 2017b; Shah et al 2020; Tanase et al 2019; Thomas et al 2006; Tomasoni et al 2019; Volpe et al 2016; Yamaguchi et al 2004; Zile et al 2013).

Pro-inflammatory biomarkers (TNFα, CRP, PTX3, IL6) are increased in HFpEF. Higher levels are observed in acutely decompensated HFpEF and are associated with an inflammatory systemic syndrome and echocardiographic Doppler parameters of diastolic dysfunction, Pentraxin3 (PTX3) has been correlated with LAVI. Plasma levels of BNP, proBNP, NTproANP and troponin I are significantly higher in HFrEF in comparison with HFpEF. Structural changes in HFpEF, like focal fibrosis is correlated with galectin3, GDF-15, MMP-3, MMP-7, MMP-8, BNP, pro-BNP and NTproANP levels and diffuse fibrosis with GDF-15, Tenascin-C, MMP-2, MMP-3, MMP-7, BNP, proBNP and NTproANP (Abernethy et al 2018; Kanagala et al 2020; Remmelzwaal et al 2020; Shah et al 2016; Yu et al 2013).

C-reactive protein (CRP), interleukin-6(IL6), tumor necrosis factor receptor-1(TNFR-1), Cystatin-C and neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinases (TIMP-1, TIMP-4), matrix metalloproteinases (MMP-2, MMP-3, MMP-7, MMP-8, MMP-9), pro-BNP, N-terminal pro-atrial natriuretic peptide (NTpro-ANP), galectin3, suppression of tumorigencity-2 (ST2) are associated with LV hypertrophy, cardiac remodelling, LA wall stress/ stretch and kidney dysfunction. These biomarkers might be considered prognostic biomarkers in HFpEF (Abernethy et al 2018; Kanagala et al 2020; Remmelzwaal et al 2020; Shah et al 2016).

CRP (C-reactive protein)

CRP is an inflammatory biomarker correlated with systemic inflammatory syndrome. Increased CRP plasma levels are associated with cardiomyocyte stress/damage, LV hypertrophy and LA wall stress/stretch, diastolic dysfunction and myocardial remodeling in HFpEF. CRP is also considered a prognostic biomarker for HFpEF clinical characteristics, severity, pulmonary hypertension (PH) and associated comorbidities (DuBrock et al 2018; Gevaert et al 2017; Ho et al 2019; Jirak et al 2020; Kanagala et al 2020; Mocan et al 2019; Shah et al 2016; Shah et al 2018; Simmonds et al 2020).

Interleukins (IL1/IL6 / IL 11/IL 33)

High sensitive Troponin-I, BNP and galectin-3 are significant predictors of future new onset HFpEF, while IL6 and sST2 can't be considered predictive biomarkers of future development of HFpEF (Bayes-Genis et al 2020; Michalska-Kasiczak et al 2018; Watson et al 2021).

Patients diagnosed with HFpEF have higher levels of soluble interleukin 1 receptor-like 1 (IL1RL1), CRP, IL6 and growth differentiation factor-15 (GDF-15) than patients with HFrEF (DuBrock et al 2018; Gevaert et al 2017; Jirak et al 2020; Kanagala et al 2020; Markousis-Mavrogenis et al 2019; Shah et al 2016; Shah et al 2018).

IL6 and intercellular adhesion molecule 1 (ICAM1), as well as increased protein levels of tumor necrosis factor (TNF) are correlated with cardiac fibrosis in HFpEF (Bai et al 2019; Kolijn et al 2020; Sabbah et al 2020).

IL11 is a member of the IL6 family of cytokines, but has distinct properties from other family members. The recombinant human heart IL11 (rhIL11) is considered a cardioprotective and antifibrotic biomarker. Research studies showed that administration of recombinant mouse IL11 is strongly profibrotic. Circulating levels of IL11 are elevated in patients with HF and correlated with with poor clinical outcome in CHF, HF progression and worsening of HF symptoms and with cardiovascular events including HF hospitalization, stroke and mortality rate (Sweeney et al 2020; Webber et al 2020; Ye et al 2019).

IL6 is a biomarker associated with inflammatory systemic syndrome, effects of IL-6 signaling in the failing heart are primarily pro-inflammatory and can exacerbate heart dysfunction, elevated IL6 levels are associated with to chronic inflammation and fibrotic disorders. IL6 might be considered a potential therapeutic target in HF in developing novel therapeutic strategies in HF. IL6 serum levels in HF patients may be considered predictive biomarker of poor clinical outcomes and a powerful prediction biomarker of LV remodelling (Bai et al 2019; de Boer et al 2018; DuBrock et al 2018; Fontes et al 2015; Kobara et al 2010; Kolijn et al 2020; Markousis-Mavrogenis et al 2019; Sweeney et al 2020).

Administration of an anti-IL6R antibody improved LV function in heart failure post-infarction highlighting its therapeutic potential (Fontes et al 2015; Hanna et al 2020; Hartman et al 2016; Kobara et al 2010).

IL10 is highly correlated with diastolic dysfunction and cardiac fibrosis. IL10 might represent also a therapeutic target in patients with HFpEF-related LA dysfunction (Bode et al 2020; Cihakova 2018; Hulsmans et al 2018; Sziksz et al 2015).

IL33 is member of the interleukin-1 (IL-1) family and has the potential of a cardioprotective biomarker with antifibrotic and antihypertrophic effect. IL33 is a potential diagnostic biomarker in HFpEF and therapeutic target in HF and might have important role in cardio prevention strategies (Chen et al 2015; Garbern et al 2019; Jirak et al 2020; Michalska-Kasiczak et al 2018; Schmitter et al 2014; Zordoky et al 2015).

GDF 15 (growth differentiation factor)

GDF15 is a pleiotropic protein, a member of transforming growth factor β family (TGF β), involved in different biologic processes: inflammation, cell cycle, apoptosis. It is secreted by adipocytes, macrophages, the endothelium and smooth muscle as result of inflammatory stress. GDF-15 is an independent predictor of LV hypertrophy in hypertensive patients. GDF-15 is correlated with the E/e' ratio and represents at least as good as NT-proBNP biomarker for the detection of HFpEF and the combination of both markers was better than NT-proBNP alone. GDF-15 therapy provided independent prognostic information in HF, NT-proBNP:GDF15 ratio provide differential diagnosis between HFpEF and HFrEF, GDF-15 allows risk stratification of patients with chronic HFrEF (Adela et al 2015; Berezin 2016; D'Amario et al 2019; Meluzin et al 2015; Michalska-Kasiczak et al 2018; Rochette et al 2021; Santhanakrishnan et al 2012; Schmitter et al 2014; Sharma et al 2017; Stolina et al 2020; Upadhya, Pisani, et al 2017; Wesseling et al 2020).

The secretion of GDF 15 is also induced by Angiotensin II, mechanical stress, ischaemia and inflammatory cytokines. Circulating GDF-15 levels are correlated with age, insulin resistance, and creatinine might provide additional prognostic cardiovascular information of GDF-15 compared to known risk factors (Arkoumani et al 2020; Gulsin et al 2019; Kempf et al 2006; Kempf et al 2009; Rochette et al 2021; Sharma et al 2021; Vila et al 2011).

GDF15 levels are correlated with advanced age, advanced HFpEF stage, worse cardiac remodeling processes (NYHA class), inflammatory response and adverse cardiac events in chronic heart failure (Berezin 2016; Eyre et al 2016; Meluzin et al 2015; Rochette et al 2021; Santhanakrishnan et al 2012; Sharma et al 2017; Wesseling et al 2020).

GDF 15, H-FABP, sST2, and soluble urokinase-type plasminogen activator receptor (suPAR) are important diagnostic and severity/progression HF biomarkers in HFpEF (Berezin 2016; D'Amario et al 2019; Jirak et al 2020; Meluzin et al 2015; Rullman et al 2020).

GDF15 level is higher in patients with T2DM compared with those without T2DM, highlighting a different pathogenetic mechanisms involved in HFpEF. GDF-15 might represent a therapeutic target in developing novel therapeutic strategies for diabetic and cardiovascular diseases. GDF 15 increased levels are correlated with E/e′ ratio in HFpEF patients (Adela et al 2015; Baessler et al 2012; Chung et al 2020; Gulsin et al 2019; Meluzin et al 2015; Wesseling et al 2020). GDF15, proBNP and troponin T increased levels are associated with high hospitalization rates and cardiovascular mortality (Chan et al 2016; Damman et al 2014; Rochette et al 2021; Rullman et al 2020; Santhanakrishnan et al 2012; Sharma et al 2017; Wesseling et al 2020).

GDF15 is considered a biomarker for therapeutic interventions in HFpEF precise medicine. Studies proved that GDF 15 targeted treatments improved exercise capacity in HF patients (Adela et al 2015; Shah 2017b; Sharma et al 2021; Sharma et al 2017; Stolina et al 2020; Wesseling et al 2020).

Pentraxin 3 (PTX3)

PTX3 is an acute phase protein produced in the coronary circulation in patients with LVDD.

PTX3 is considered a prognostic biomarker which is correlated with endothelial dysfunction, systemic inflammation and HFpEF pathophysiology, diastolic dysfunction in subclinical HFpEF and HFpEF mortality rate (Carnes et al 2020; Carrizzo et al 2015; Dubin et al 2012; Kaess et al 2011; Kanagala et al 2015; Matsubara et al 2014; Matsubara et al 2011; Ristagno et al 2019).

PTX3 is considered an independent prognostic biomarker for adverse cardiac events, also correlated with NYHA stage (Dubin et al 2012; Fornai et al 2016; Kaess et al 2011; Kanagala et al 2015; Matsubara et al 2014; Matsubara et al 2011).

PTX3 modulates inflammatory response, decreases vascular inflammation and atherosclerosis and is involved in myocardial remodeling processes and might be considered prognostic biomarker of cardiovascular events (Carrizzo et al 2015; Casula et al 2017; Fornai et al 2016; Kaess et al 2011; Kanagala et al 2015; Matsubara et al 2011; Norata et al 2010; Norata et al 2009; Shiraki et al 2016; Zlibut et al 2019).

Increased PTX 3 levels are correlated with HFpEF, LV diastolic dysfunction, increased LV filling pressures or increased wall tension but can't differentiate HFpEF from HFrEF (Carrizzo et al 2015; Kaess et al 2011; Matsubara et al 2011).

Circulating levels of PTX3, tumor necrosis factor-alpha (TNFα), and IL-6 are significantly increased in HFpEF. PTX3 might be considered a useful biomarker for assessment of risk stratification in HFpEF (Carnes et al 2020; Kaess et al 2011; Kanagala et al 2015; Matsubara et al 2014; Matsubara et al 2011).

vWf (von Willebrand factor)

von Willebrand factor (vWF) is a protein released in response to endothelial injury. It is involved in hemostasis and inflammatory activation and might be considered an independent prognostic biomarker for long-term outcome in patients with HFpEF correlated with endothelial dysfunction as potential mediator in the pathophysiology of HFpEF, also potential biomarker for risk assessment in patients with HFpEF (Gragnano et al 2017; Kleber et al 2015; Meijers et al 2016; van de Wouw et al 2019).

vWF, as well as GDF-15, cystatin C, resistin are associated with myocyte stress, inflammation and cardiac remodeling in HFpEF (Meijers et al 2016; van de Wouw et al 2019).

Circulating levels of vWF are correlated with microalbuminuria in patients with essential hypertension. vWF and NT-proBNP improved risk prediction in HFpEF and, both biomarkers are considered independent prognostic biomarkers of mortality in heart failure patients (Calvier et al 2013; Kleber et al 2015; Meijers et al 2016).

Galectin3

Galectin3 is a member of galactoside-binding lecitins, secreted by activated macrophages, involved in myocardial inflammation, fibroblast proliferation, cardiac fibrosis, diastolic dysfunction and cardiac remodelling. Galectin 3 is mainly a cardiac fibrosis biomarker involved in HFpEF pathogenesis, which is strongly correlated with LV hypertrophy, diastolic dysfunction and cardiac remodeling and therapeutic target in cardiac remodeling and heart failure (Calvier et al 2013; de Boer et al 2009; de Boer et al 2010; Yancy et al 2013; Yu et al 2013).

Galectin3 has prognostic value in acute or chronic heart failure onsetting, being also correlated with increased hospitalization rate and high mortality rate (Beltrami et al 2016; de Boer et al 2009; de Boer et al 2010; Edelmann et al 2015; Shah et al 2010; Yancy et al 2013).

Circulating levels of galectin 3 are correlated with age and kidney dysfunction. Galectin3 mediates aldosterone induced fibrosis and vascular fibrosis in HF development, progression and cardiac remodeling and it can be considered a useful biomarker for risk stratification in HF and also a therapeutic target in prevention or reversal of heart failure with extensive fibrosis. Its diagnostic value for the acute onset of HF is considered inferior to NT-proBNP (Calvier et al 2013; de Boer et al 2009; de Boer et al 2010; Polat et al 2016; Yancy et al 2013; Yu et al 2013).

Galectin3 gene controls fibroblast activation and procollagen expression. Galectin 3 might represent a useful therapeutic target in developing novel therapeutic strategies in HFpEF, which might provide a better control of cardiac remodeling. Therapeutic molecules binding to galectin-3 might represent potential therapeutic candidates for cardiac prevention or control/ reversal of fibrosis processes in heart failure (Calvier et al 2013; de Boer et al 2009; Yu et al 2013). Galectin-3 is still considered a

controversial biomarker due the interference with kidney function and its multi-organ source (Calvier et al 2013; Chen et al 2016; de Boer et al 2009; Tan et al 2018; Yu et al 2013).

Cystatin C

Cystatin C(CyC) is a biomarker of renal dysfunction, defined by increased serum levels of creatinine or cystatin-C. High levels of CyC are associated with HFpEF development and are correlated with diastolic dysfunction, LV hypertrophy in HFpEF, myocardial fibrosis and structural cardiac changes (interventricular septal thickness, posterior wall thickness and LVMI) and might be a prognostic biomarker for cardiovascular outcomes (Bishu et al 2012; Carrasco-Sanchez et al 2011; Huerta et al 2016; Ix et al 2006; Michalska-Kasiczak et al 2018; Nosaka et al 2013; Schmitter et al 2014; Wan et al 2016).

CyC circulating levels are also correlated with left atria dimensions in different stages of diastolic dysfunction, associating poorer outcome of these patients (Chen et al 2019; Ix et al 2006; Nosaka et al 2013).

Increased CyC levels are correlated with a high risk of developing HFpEF in patients with coronary artery disease without signs of heart failure (Chen et al 2019; Ix et al 2006; Michalska-Kasiczak et al 2018; Nosaka et al 2013).

In hypertensive patients with HFpEF, CyC levels are associated with diastolic dysfunction and myocardial fibrosis. Cystatin C is considered a biomarker for hypertensive LV hypertrophy and myocardial fibrosis via accumulation of osteopontin and TIMP-1 (Huerta et al 2016; Ix et al 2006; Michalska-Kasiczak et al 2018; Mocan et al 2019; Nosaka et al 2013).

CyC is a prognostic biomarker of cardiovascular outcome and adverse cardiac events in HFpEF patients, its high levels being correlated with the hospitalization rate in HFpEF, independently of creatinine levels or glomerular filtration rate (Abernethy et al 2018; Carrasco-Sanchez et al 2011; Chen et al 2019; Huerta et al 2016; Ix et al 2006; Michalska-Kasiczak et al 2018; Nosaka et al 2013; Wan et al 2016).

CyC circulating levels are also associated with therapy response, beeing an useful biomarker in therapeutic management (Chen et al 2019; Michalska-Kasiczak et al 2018; Shlipak et al 2005; Wan et al 2016).

Increased CyC levels correlate with the risk of developing HFpEF and with a higher risk of all cause mortality in HF patients (Chen et al 2019; Shlipak et al 2005).

MMP/TIMP (Matrix metalloproteinases/ tissue inhibitors of metalloproteinases)

Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) are prognostic biomarkers for cardiac fibrosis, cardiac hypertrophy and LVDD in HFpEF (Kanagala et al 2020; Krebber et al 2020; Mocan et al 2019; Shear 2019; Simmonds et al 2020).

MMP2, MMP9, TIMP 1 are strongly associated with cardiac fibrosis and cardiac remodeling. MMPs and TIMPs can control remodeling processes based on the type of micro-environment. TIMP2 controls cardiac fibroblasts activity in correlation with the tissue microenvironment. TIMP 2 and TIMP1 might become a therapeutic target for the development of novel therapeutic options which might attenuate postinjury cardiac remodeling and control cardiac fibrosis (Eiros et al 2020; D. Fan et al 2012; Graziani et al 2021; Henning 2020; Kanagala et al 2020; Krebber et al 2020; Ngu et al 2014; Shear 2019; Simmonds et al 2020; Upadhya & Kitzman 2017).

While some studies show similar levels of MMP 9 in HFrEF and HFpEF, other studies reveal higher MMP9 and MMP2 levels in HFrEF. Decreased MMP and TIMPs levels are correlated with LV stiffness (Carrick-Ranson et al 2019; Pan et al 2020; Shear 2019; Simmonds et al 2020).

Soluble suppression of tumorigenicity 2 (sST2), MMP-2 and MMP-9 are associated with cardiac remodeling and tissue fibrosis in HF and might be considered independent risk factors for patients with heart failure (Ngu et al 2014; Pan et al 2020; Upadhya & Kitzman 2017).

Decreased levels of MMP-1 and the tissue inhibitor of MMP-1 are correlated with myocardial fibrosis especially in HFpEF and arterial hypertension. Increased carboxy-terminal propeptide of procollagen type-I (PICP) and low serum carboxy-terminal telopeptide of collagen type I to matrix metalloproteinase-1 ratio (CITP: MMP-1) are correlated with chronic kidney disease in hypertensive patients diagnosed with HFpEF. Myocardial MMPs and TIMPs, enhance myocardial renin-angiotensin system imbalance and cardiac fibroblast synthesis, also secretion of IL-10, an anti-fibrotic cytokine involved in cardiac fibrosis and cardiac remodeling (Eiros et al 2020; Humeres et al 2019).

ST2 (Suppression of tumourigenicity 2)

ST2 is a member of IL1 family and has 2 isoforms: soluble form (s ST2) and transmembrane ST2 (ST2L) with different effects on cardiovascular system. ST2 is the ligand for IL33 and mediates the cardioprotective effects, while sST2 inhibits the cardioprotective effects of IL33 by binding competition with IL33 (Cui et al 2018; Michalska-Kasiczak et al 2018; Miftode et al 2021; Sanada et al 2007; Schmitter et al 2014; Seki et al 2009; Shah et al 2016; Zach et al 2020).

sST2, MMP-2 and NT-proBNP are considered independent risk factors for patients with heart failure. sST2 and Galectin 3 are associated with fibrosis extension and the severity of HFpEF and they might represent useful biomarkers for positive diagnosis/early stage of HFpEF and a prognostic biomarker for HFpEF severity and adverse cardiac events. ST2 is correlated with myocardial fibrosis and poor outcome in patients with HF (Cui et al 2018; Dalal et al 2018; Farcas et al 2020; Michalska-Kasiczak et al 2018; Miftode et al 2021; Pan et al 2020; Parikh et al 2016; Schmitter et al 2014; Shah et al 2016).

sST2, GDF-15, galectin 3, IL1 and IL6 are correlated with diastolic dysfunction and echocardiographic parameters in HFpEF (Cui et al 2018; Michalska-Kasiczak et al 2018; Mocan et al 2019; Tanase et al 2019).

ST2 is a prognostic biomarker in HFpEF associated with clinical features and therapeutic response of these patients (Michalska-Kasiczak et al 2018; Najjar et al 2019; Schmitter et al 2014; Zach et al 2020).

Increased sST2 levels are associated with increased cardiovascular mortality but also an important prognostic factor in patients diagnosed with COVID-19 (Farcas et al 2020; Miftode et al 2021; Pan et al 2020; Parikh et al 2016; Schmitter et al 2014; Shah et al 2016; Zach et al 2020).

ST2L/IL-33 interaction represents a complex cardioprotective biochemical mechanism with preventive role in hypertrophic

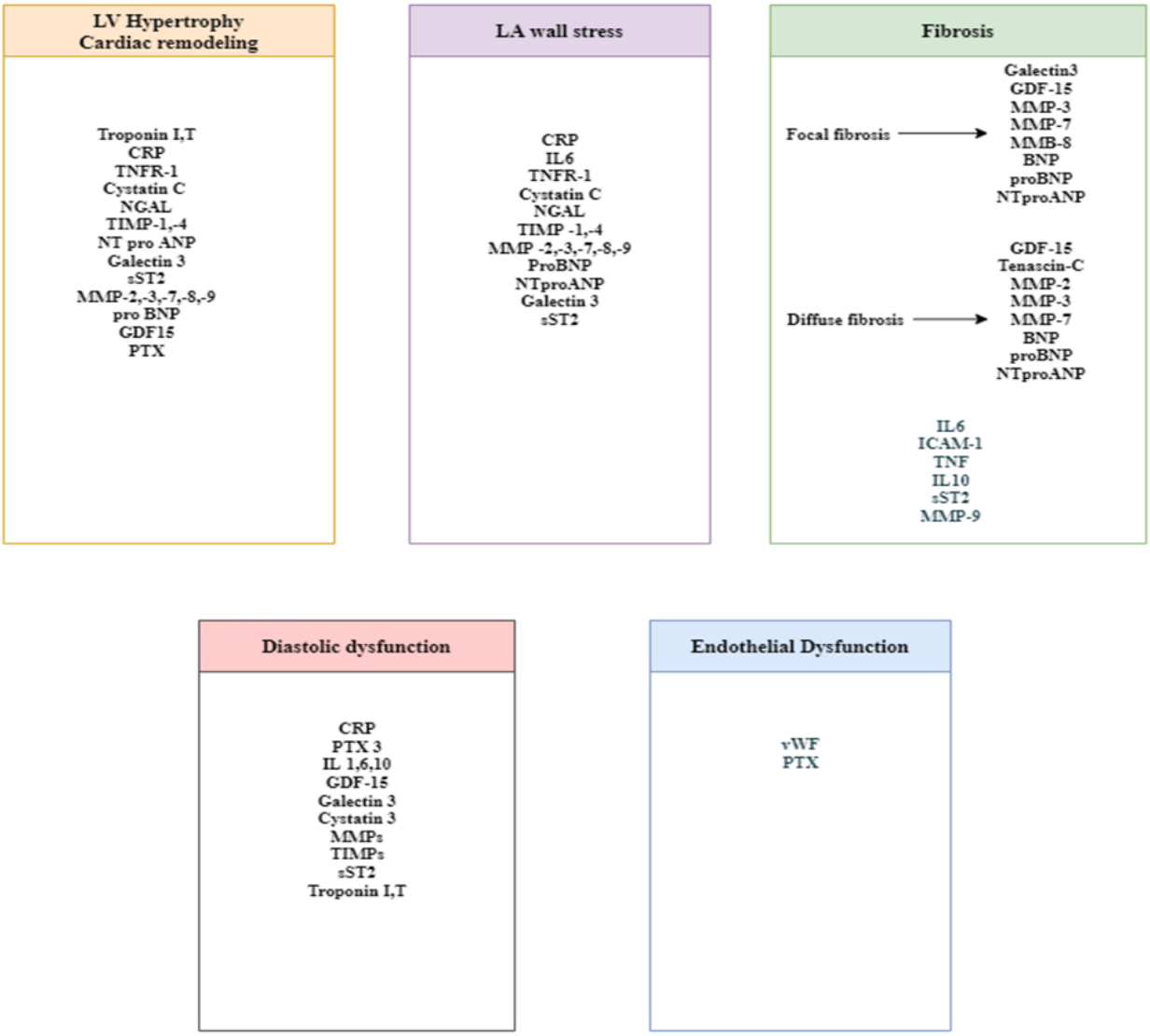

Figure 1. Biomarkers and their pathogenetic implication in HF

and fibrotic processes and protects myocytes from apoptosis. (Zach et al 2020) This property might be explored in cardio prevention research studies in order to decrease HFpEF incidence, to prevent cardiac fibrosis and extensive remodeling processes in HFpEF and improve clinical outcome and survival rates of these patients (Cui et al 2018; Michalska-Kasiczak et al 2018; Miftode et al 2021; Parikh et al 2016; Schmitter et al 2014; Shah et al 2016; Zach et al 2020).

Research studies proved that ST2 diagnostic value is similar with BNP, but inferior to NT-proBNP and MR proANP (Cui et al 2018; Dalal et al 2018; Michalska-Kasiczak et al 2018; Schmitter et al 2014; Shah et al 2016).

In conclusion, ST2 has still a limited diagnostic value in HF, but it can be an important biomarker in cardio prevention strategies and HFpEF therapeutic strategies (Cui et al 2018; Dalal et al 2018; Farcas et al 2020; Michalska-Kasiczak et al 2018; Miftode et al 2021; Pan et al 2020; Parikh et al 2016; Schmitter et al 2014; Shah et al 2016; Tanase et al 2019; Zach et al 2020).

In table 1 we summarized the clinical and therapeutic implications of functional biomarkers in HFpEF.

Molecular biomarkers

Single nucleotide polymorphisms (SNPs)

Recent research studies in medical genetics describe molecular biomarkers which are involved in molecular pathways of HF pathogenesis, progression or therapy response (Bielecka-Dabrowa et al 2017; de Denus et al 2018; Kao et al 2017; Zhang et al 2019).

CYP3A4 inferred phenotype is correlated with peak sildenafil dose-adjusted concentrations in patients with HFpEF receiving high doses of sildenafil. Molecular profile can influence sildenafil's hemodynamic effects in patients with pulmonary hypertension or its efficacy in treating erectile dysfunction (de Denus et al 2018; Peskircioglu et al 2007).

SNPs of TGFBR3 (rs6696224), NRG1 (rs2466052), ELN (rs3823879), CALM1 (rs5871), BCL9 (rs604983), CYP24A1 (rs2762941) and ARHGEF1 (rs882520) are strongly correlated with the risk of developing HFpEF. TGFB3 rs6696224 is involved in HFpEF pathogenesis, correlated with HF incidence and its clinical profile. TGFBR3 might be considered a therapeutic target in HFpEF personalized medicine experimental research studies, while rs3917187 polymorphism, an intron variant of

Table 1. Diagnostic, prognostic and therapeutic significance of functional biomarkers in HFpEF

Biomarkers	Diagnostic	Prognostic	Therapeutic	Prevention/ cardioprotection
NP	+	++	+	
TROPONINS	+	+		
CRP	+	+	+	
IL6	+	+	+	
IL 10		+	+	
IL 11		+	+	
IL33			+	+
GDF 15	+	+	+	
PTX3	+	+		
vWF		+		
Galectin 3		+	+	+
Cystatin C	+	+	+	
MMP/ TIMP		+	+	
ST2		+	+	+

the TGFB3 gene encoding TGF-β3 is correlated with LVMI and LV dimensions (Hu et al 2010; Kao et al 2017).
Rs6696224, rs2466052, and rs3823879 were significantly associated with HFpEF (Bielecka-Dabrowa et al 2017; Hage et al 2020; Kao et al 2017; Zhang et al 2019).
Apolipoprotein L1 (APOL1) genotypes were associated with HFpEF hospitalization rate, especially in patients with renal dysfunction (Franceschini et al 2018; Grams et al 2019; Zhang et al 2019).
ALDH2*2 variants, atrial fibrillation, age and anaemia are also correlated withHFpEF development (Pang et al 2017; Xia et al 2020; Zhang et al 2019).
SNPs might be considered diagnostic, prognostic tools or therapeutic targets in this type of heart failure (Bielecka-Dabrowa et al 2017; de Denus et al 2018; Kao et al 2017; Zhang et al 2019).

ACE I/D

ACE genetic polymorphisms were studied a long ago, being involved in HF pathogenesis, therapy response and clinical outcome of HF patients. In hypertensive patients D allele of ACE gene is associated with LV hypertrophy (which associates poor outcome, myocardial infarction, stroke and cardiovascular deaths) in HFpEF patients. This genetic polymorphism might be considered a predictive biomarker for HFpEF diagnosis. In hypertensive patients, D allele of ACE gene is correlated with increased LVMI, diastolic dysfunction in HFpEF, highlighting the role of ACE genetic polymorphisms in HFpEF pathogenesis and progression (Arendse et al 2019; Bahramali et al 2016; Cosenso-Martin et al 2015; Fajar et al 2019).
D allele of ACE gene is associated with high risk of developing HFpEF, especially in hypertensive patients, but it's also a prognostic biomarker for risk stratification and a therapeutic target. DD genotype is correlated with diastolic dysfunction and I/D ACE genotype is correlated with functional capacity and physical performance of HFpEF patients. ACE genetic polymorphisms allows the description of different molecular pathways in HFpEF and HFrEF. Genetic polymorphisms ACE G2350A, rs4291 and rs4343 are correlated LVH with high risk of developing HFpEF (Arendse et al 2019; Bahramali et al 2017; Bahramali et al 2016; Krittanawong et al 2017).

miRNAs

MiRNAs are small RNAs (18-22 nucleotides) which control/ reduce expression of targeted proteins. MiRNAs are involved in the regulation of cardiac and vascular function and define molecular mechanisms involved in HFpEF pathogenesis (Henkens et al 2020; Kriegel et al 2017; Schmitter et al 2014; Schulte et al 2015; Zhou et al 2018).
Frequently circulating miRNAs are associated with different comorbidities, independent of myocardial disease in HFpEF. Studies proved that patients with diabetes mellitus, increased levels of ***miRNA-9, - 126, -370*** are found in presence of coronary artery disease, while ***miRNA-21-5p*** is associated with fibrosis, autoimmune diseases and inflammation. ***MiR-126, miR-130b, miR-223*** and ***miR-660*** are correlated with diabetic nephropathy and microvascular injury. ***miRNA-423-5p, miR-320a, miR-22,*** and ***miR-92b*** might be considered useful diagnostic biomarkers in chronic heart failure, while plasma levels of ***miR-34a, miR-192,*** and ***miR-194*** are elevated in HF due to acute myocardial infarction. ***miR-423-5p*** might be considered a useful biomarker in HF diagnosis, being correlated with the severity of heart failure, but not with LVEF and NYHA class, ***miR-660-3p, miR-665,*** and ***miR-1285-3p*** are correlated with LVEF (Ali Sheikh et al 2016; Florijn et al 2020; Halushka et al 2019; Kriegel et al 2017; Schmitter et al 2014; Schulte et al 2015; Wu et al 2018).
Increased levels of ***miR-423-5p, miR-18b, miR-129-5p, miR-1254, miR-622*** are correlated with NYHA functional class, miR-210 expression is correlated with with NYHA III and IV, and increased levels of ***miR-499, miR-122,*** especially ***miRNA-499*** are correlated with acute myocardial infarction and acute heart failure (Barile et al 2017; Busch et al 2016; Rech et al 2018; Schmitter et al 2014; Schulte et al 2015; Wu et al 2018; Zhang et al 2015).
MiR-208 is involved in the regulation of cardiac hypertrophy, cardiac remodeling and might represent useful therapeutic target

for the modulation of cardiac function and cardiac remodeling during heart disease progression. ***MiRNA-208*** over expression is correlated with inhibition of cardiac fibrosis, but as regulator of endoglin might also promote cardiac fibrosis and remodeling processes (Callis et al 2009; Da Costa Martins et al 2012; Divakaran et al 2008; Schmitter et al 2014; Schulte et al 2015). ***MiR-1, miR-21, miR-133, miR-195, -208*** are involved in regulation of cardiac hypertrophy. (Cai et al 2010; Da Costa Martins et al 2012; Dong et al 2014; Hang et al 2016; Kura et al 2020; Schmitter et al 2014; Schulte et al 2015) ***MiRNA-133*** and ***miR-590*** decrease fibroblast activity and collagen production, but administration of antisense oligonucleotides against ***miR-133*** or ***miR-590*** inhibit this cardioprotective effect (Li et al 2018; Schulte et al 2015; Shan et al 2009; Yuan et al 2020).

MiR-21 is a key regulator of cardiac fibrosis, cardiac remodeling and hypertrophy in HFpEF by up-regulating the expression of the anti-apoptotic gene Bcl-2 Silencing ***miR-21*** by antagomiRs lead to cardiomyocytes necrosis and apoptosis highlighting its role in cardiac remodeling. Increased expression of ***miR-24, miR-125b, miR-195, miR-199a***, ***miR-214*** and ***miR-155*** are correlated with adverse cardiac remodeling process and worse cardiac structure in HF, also intramyocardial ***miR-24*** increased levels are correlated with decreased fibrosis processes in the myocardial infarction border areas and might be considered as target for treatment of myocardial infarction and fibrotic heart disorders (Fernandes et al 2011; Rech et al 2018; Schulte et al 2015; Wang et al 2012).

MiR-145 is correlated with LV remodeling and can be used as therapeutic target to prevent adverse cardiac remodeling after myocardial infarction (Liu et al 2020; Schulte et al 2015; Song et al 2020; Wu et al 2018).

MiRNAs are promising biomarkers in HFpEF diagnosis, prognostic and personalized therapeutic strategies (Chen et al 2019; Florijn et al 2020; Halushka et al 2019; Henkens et al 2020; Kriegel et al 2017; Schmitter et al 2014; Schulte et al 2015).

Increased ***miR-1*** and ***miR-133*** levels are correlated with inhibition of cardiac hypertrophy (Care et al 2007; Dong et al 2014; Li et al 2018; Schulte et al 2015).

Circulating levels of ***miR-34a, -224 and -452*** are frequently correlated with HFpEF and diastolic dysfunction. ***miR-30c, −146a, −221, −328,*** and ***−375*** can be useful diagnostic biomarkers for HFpEF alone or in combination with natriuretic peptides (Barile et al 2017; Florijn et al 2020; Rech et al 2018; Schulte et al 2015; Watson et al 2015) and **exo**-***miR-92b-5p*** is considered a diagnostic biomarker for HFrEF, while ***hsa-miR-193a-5p, hsa-miR-30a-5p, hsa-miR-106a-5p, hsa-miR-191-5p, hsa-miR-486-5p, hsa-miR-181a-2-3p, hsa-miR-660-5p,*** and ***hsa-miR-199b-5p*** are correlated with HFpEF (Chen et al 2019; Wu et al 2018).

MiR-146a is a cardio protection biomarker involved in antifibrotic processes (Barile et al 2017; Jakubik et al 2021; Nazari-Shafti et al 2020; Rech et al 2018; Schulte et al 2015; Watson et al 2015).

MiR-126 plays an important role in endothelial homeostasis and vascular integrity. ***miR-126*** levels are decreased in associated comorbidities like diabetes with microvascular dysfunctions and might be considered as a microvascular dysfunction biomarker and associated with microvascular coronary endothelial dysfunction. Restoration of endothelial ***miR-126*** levels in microvascular dysfunctions provide novel therapeutic approaches in HFpEF management (Barile et al 2017; Chen et al 2019; Florijn et al 2020; Kriegel et al 2017; Pei et al 2020; Rech et al 2018; Schulte et al 2015; Wang et al 2008; Watson et al 2015; Wu et al 2018).

Cardio protection

Describing molecular pathways involved in HF pathogenesis, genetic variants and miRNAs involvement in cardiac fibrosis, remodeling processes and clinical outcome, future research studies will define cardio protection biomarkers in order to develop novel cardio prevention programmes, decrease HF incidence, provide early diagnostic and optimize therapeutic response and improve quality of life and survival rates in patients diagnosed with HFpEF. ***miR-1*** up regulation and ***miR-21*** cardioprotective effects via PTEN/Akt pathway can remote ischemic preconditioning in long-term ischemia. Cardiac progenitor cell (CPC)-derived exosomes are enriched in cardioprotective microRNAs, especially ***miR-146a-3***p or circulating exosomes might provide cardio protection after ischemia/reperfusion injury (Barile et al 2017; He et al 2021; Jakubik et al 2021; Kura et al 2020; Nazari-Shafti et al 2020; Rech et al 2018; Saludas et al 2021; Schmitter et al 2014; Schulte et al 2015; Watson et al 2015).

Current experimental studies aim to define exosomes as diagnostic biomarkers in cardiovascular disorders (Barile et al 2017; Femmino et al 2020; Wu et al 2018).

miRNA- miR-21, -27a, -29a, -155, -210,1, 142,150, 133a/b. 146a, 423 are useful biomarkers for novel therapeutic options or screening programs in heart failure in correlation with NT-proBNP and NYHA class. IL33 is a possible cardio-prevention biomarker by its antihypertrophic and antifibrotic effect. ST2/IL33 interaction and its role in controlling cardiac remodeling, fibrotic and hypertrophic effects, beside Galectin 3 targeted therapies, might provide also cardio prevention opportunities (Busch et al 2016; Chow et al 2017; Cui et al 2018; Ghantous et al 2020; Michalska-Kasiczak et al 2018; Miftode et al 2021; Parikh et al 2016; Schmitter et al 2014; Shah et al 2016; Zach et al 2020).

MiR-1 and ***miR-21*** proved also a cardioprotective role, being also antagomirs designed to functionally inhibit ***miR-21*** significantly reduced cardiac hypertrophy and fibrosis and improved cardiac function (Busch et al 2016; C. H. Chen et al 2019; Dai et al 2020; Dong et al 2014; Femmino et al 2020; Ghantous et al 2020; Kura et al 2020; Saludas et al 2021; Schmitter et al 2014; Schulte et al 2015; Wu et al 2018).

Novel molecular biomarkers might be considered diagnostic, prognostic but also therapeutic targets in developing innovative therapeutic strategies in HFpEF, providing a better therapy response and control of associated comorbidities or HFpEF progression. Antagomirs might be considered useful therapies to prevent or reverse cardiac hypertrophy and improve cardiac function in heart failure patients, therapeutic inhibition of TGFβ also might provide the control of cardiac fibrosis and remodeling in these patients (Chow et al 2017; Z. Fan et al 2016; Gaze 2007; Kura et al 2020; McHugh et al 2019; Michels da Silva et al 2019; Parichatikanond et al 2020; Patel et al 2019; Schmitter et al 2014; Schulte et al 2015; Shah 2017a; Shear 2019; Sweeney et al 2020; Wintrich et al 2020; Yousefi et al 2021).

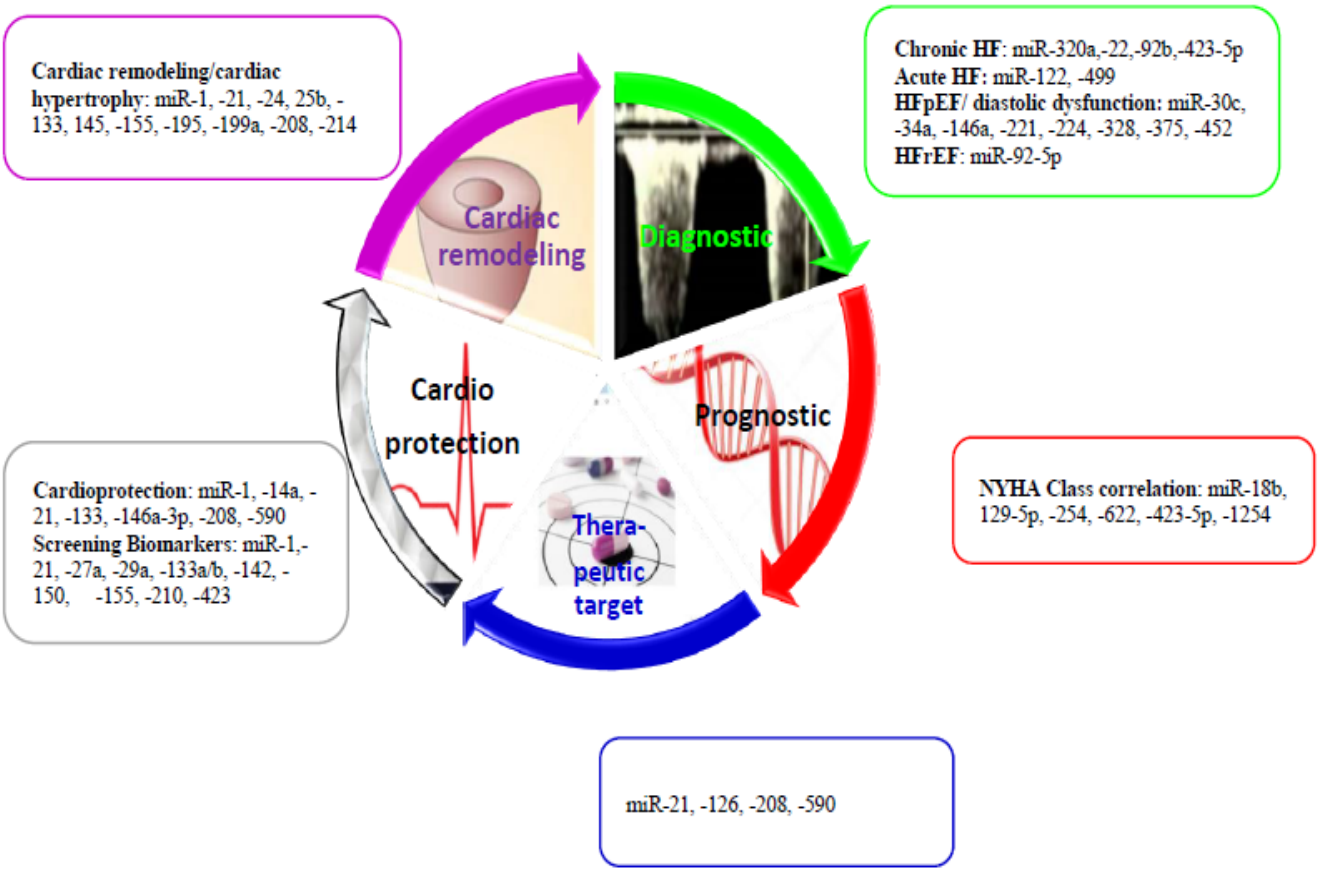

Figure 2. MiRNAs in HFpEF

Conclusions

Progresses of functional genomics, medical genetics and experimental studies in cardiology will provide novel biomarkers for positive diagnosis, prognostic and monitoring therapy response and clinical outcome or therapeutic targets for precise therapy in HFpEF. Novel molecular biomarkers in a multi biomarker combined strategy will provide accurate early diagnosis, evaluate therapy response and personalized therapy which will improve survival rates and quality of life in HFpEF patients. Targeting molecular pathways, miRNAs involved in cardiac fibrosis and HFpEF pathogenesis and progression will provide novel therapeutic strategies but also cardio prevention options in this pathology.

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