Biomarkers of Heart Failure with Preserved and Reduced Ejection Fraction

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Abstract

Biomarkers are increaingly being used in the management of heart failure not only for the purpose of screening, diagnosis, and risk stratification, but also as a guide to evaluate the response to treatment in the individual patient and as an

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entry criterion and/or a surrogate marker of efficacy in clinical trials testing novel drugs. In this chapter, we review the role of established biomarkers for heart failure management, according to the main classification of HF phenotypes, based on the measurement of left ventricular ejection fraction, including heart failure with reduced (<40%), preserved (≥50%), and, as recently proposed, mid-range (40-49%) ejection fraction.

1   Introduction

Early diagnostic and therapeutic interventions counteracting pathophysiological mechanisms of heart failure (HF) progression, such as drugs inhibiting the renin-angiotensin-aldosterone system (RAAS) and adrenergic system activation, as well as device implantation in selected patients positively influence its clinical course, impacting on the arrhythmic burden and hemodynamics. Notwithstanding, outcome is still characterized by a high morbidity and mortality. Interest is therefore growing in the optimization of HF management and in the identification and validation of novel therapeutical tools. With these premises, research has focused on the use of biomarkers not only for the purpose of screening, diagnosis, and risk stratification, but also as a guide to the assessment of response to treatment in the individual patient, and finally as an entry criterion and/or a surrogate marker of efficacy in clinical trials testing novel drugs (Braunwald 2008; Braunwald 2013; Emdin et al. 2009).

In 2001, a National Institute of Health working group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" and identified different classes of biomarkers according to their role and potential utility in disease management. In particular, biomarkers were classified as antecedent biomarkers (i.e., those identifying the risk of developing a disease), screening biomarkers (those able to screen for subclinical disease), diagnostic biomarkers (recognizing clinically overt disease), staging biomarkers (those reflecting disease severity), or prognostic biomarkers (predicting the future course of the disease and response to pharmacological and non-pharmacological approaches) (Biomarkers Definitions Working Group 2001; Vasan 2006).

A number of biomarkers have been proposed for HF management purposes in the last years; nonetheless only a very few of them (namely B-type natriuretic peptides) are routinely used in current clinical practice. Indeed, several characteristics are requested for a circulating biomarker to be of real clinical value, related to (pre)analytical, biological, feasibility, and cost-effectiveness issues. In particular, the *ideal* biomarker for HF management should reflect the cardiovascular response to a specific pathogenic *noxa*; provide early information on

Table 1 Effects of currently recommended and previously proposed drugs for heart failure treatment on circulating levels of biomarkers

Drug class	BNP	NT-proBNP	PRC	PRA	Ang I	Ang II	Aldosterone	Gal-3	sST2	CRP	GDF-15
Beta-blockers	↑ > ↓	↑ > ↓	↓	↓	↓	↓	↓	=	↓	↓	↓?
ACEi	↓	↓	↑	↑	↑	↓	↓ / ↑	=	↓	↓	↓?
ARB	↓	↓	↑	↑	↑	↑	↓ / ↑	=	↓ / =	↓	=
MRA	↓	↓	?	↑	?	↑	↓ / ↑	=	?	=	=?
DRI	↓	↓	↑	↓	↓	↓	↓ / =	?	?	?	?
ARNI	↑	↓	↑	↑	?	↑	↓	=	=	=	?

Ang angiotensin, *ACEi* Angiotensin converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *ARNI* angiotensin receptor/neprilysin, *BNP* brain natriuretic peptide, *CRP* C-reactive protein, *DRI* direct renin inhibitor, *Gal-3* galectin-3, *GDF-15* growth differentiation factor 15, *MRA* mineralocorticoid receptor antagonists, *NT-proBNP* amino-terminal fragment of proBNP, *PRA* plasma renin activity, *PRC* Plasma renin concentration, *sST2* soluble suppression of tumorigenicity protein 2

cardiac involvement in preclinical stages (screening in HF stages A–B) and/or guide HF diagnosis when cardiac origin of symptoms is doubtful (HF stage C); be influenced by clinical modification in the disease history; and stratify patients' risk and help in therapeutic decision making (Table 1). Still, novel biomarkers are clearly required to improve risk prediction already offered by existing models, with the mere demonstration of a statistically significant association with a prespecified end-point not being enough (Pencina et al. 2008). Further to c-statistic and receiver-operating-characteristic curve (AUC) measure (Pencina et al. 2010), providing estimate of the discriminative ability of the model (i.e., the capacity to separate subject developing/not developing the outcome), and measures of calibration (indicating how close are predicted and observed risks in different groups of observations, e.g., by means of the Hosmer-Lemeshow test) and of reclassification (indicating the ability of the model to reclassify individuals into a different risk category, e.g., by calculating the net reclassification improvement, NRI) are required to adequately assess the clinical utility of novel biomarkers (McGeechan et al. 2008; Parikh and Vasan 2007).

In this chapter, current evidences on the role of established and candidate biomarkers for HF management are discussed, according to the main classification of HF phenotypes, based on the measurement of left ventricular ejection fraction (LVEF), including HF with reduced EF (HFrEF, LVEF <40%), HF with preserved EF (HFpEF, LVEF ≥50%), and the recently proposed category HF with mid-range EF (HFmrEF, LVEF 40–49%) (Ponikowski et al. 2016).

2 Biomarkers of Heart Failure with Reduced Ejection Fraction

2.1 B-type Natriuretic Peptides in Heart Failure with Reduced Ejection Fraction (HFrEF): Standing on the Shoulders of Giants

Human brain natriuretic peptide (BNP) and the amino-terminal fragment of proBNP (NT-proBNP) are produced in equimolar fashion from the cleavage of their 108-amino acid precursor proBNP by proprotein convertases, such as corin and furin. The biologically active BNP is rapidly degraded *in vivo* by several peptidases, such as dipeptidyl peptidase IV and neutral endopeptidases (NEP, neprilysin) (Clerico and Emdin 2004; Pankow et al. 2007; Vanderheyden et al. 2009). BNP, together with NT-proBNP, is mainly product of ventricular myocytes in response to increased myocardial wall stress due to volume or pressure overload states and plays a major role in HF pathophysiology, given its diuretic, natriuretic, vasodilator, and anti-hypertrophic properties (Motiwala and Januzzi 2013).

Since the beginning of the twenty-first century, several studies have accumulated showing the clinical utility of B-type natriuretic peptide testing, supporting the use of a circulating biomarker to diagnose and assess severity of HF (Januzzi et al. 2005; Maisel et al. 2002; Troughton et al. 2000). At present, BNP and NT-proBNP are routinely used for HF management in a large variety of clinical settings. Strong evidence exists supporting the use of natriuretic peptide testing to diagnose (and rule out) HF in patients presenting with dyspnea. The Breathing Not Properly and the ProBNP Investigation of Dyspnea (PRIDE) trials have shown that BNP and NT-proBNP, respectively, can diagnose HF in patients admitted to the emergency department for breathlessness, with a high accuracy and a significant negative predictive value for levels of BNP <100 ng/L (Januzzi et al. 2005; Maisel et al. 2002). Although with lower cut points, the diagnostic value of natriuretic peptides has been confirmed in ambulatory settings (Wright et al. 2003). Moreover, in a cohort of around 800 patients with chronic HF, they have been shown to be associated with the presence of LV systolic dysfunction (defined as LVEF <40%) with an AUC of 0.803 (95% CI 0.757–0.849) and 0.730 (0.681–0.778) for BNP and NT-proBNP, respectively (Moertl et al. 2009). In stable patients with HFrEF, BNP circulating levels reflect disease severity, and increase with worsening symptoms (NYHA class) (Emdin et al. 2004). The assay of natriuretic peptides is currently recommended for diagnostic purposes by all major scientific societies, including the American College of Cardiology, the American Heart Association, the Heart Failure Society of America, and the European Society of Cardiology (Lindenfeld et al. 2010; Ponikowski et al. 2016; Yancy et al. 2013); however, no single diagnostic cutoff exists and natriuretic peptide levels often fall into a "grey zone." Further, both BNP and NT-proBNP are influenced by gender, age, and comorbidities (in particular by renal function); therefore their interpretation must take into account the overall clinical assessment (Passino et al. 2008; van Kimmenade et al. 2008).

In adjunct to diagnostic properties, there is overwhelming evidence that natriuretic peptides hold prognostic value in HFrEF in both acute and chronic settings over other clinical factors. In >19,000 patients with HFrEF form the ADHERE (Acute Decompensated Heart Failure National Registry), admission BNP levels were near-linearly associated with in-hospital mortality, independently from other major clinical and laboratory risk factors (Fonarow et al. 2007). In a systematic review of studies performed in different clinical settings, Doust and colleagues have demonstrated that each 100 ng/L increase in BNP is associated with a relative 35% increase in risk (Doust et al. 2005). NT-proBNP predicts as well both short- and long-term prognosis after hospitalization for acute HF, with values >986 ng/L predicting 1-year death (Januzzi et al. 2006a, b). Although most studies have investigated the prognostic role of admission natriuretic peptide levels, there is evidence that discharge BNP and NT-proBNP, and their change during hospitalization, also predict outcome of patients with HFrEF. Data from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) show that the addition of discharge BNP to a clinical model significantly improved risk classification for 1-year mortality with an NRI of 5.5% (Kociol et al. 2011), thus suggesting that serial natriuretic peptide testing may be useful in predischarge clinical decision making (Januzzi et al. 2012). A post hoc analyses of the Valsartan Heart Failure Trial (Val-HeFT), enrolling patients with chronic symptomatic HF with LVEF <40% and LV diameter in diastole adjusted for body surface area ≥ 2.9 cm/m^2, demonstrated that BNP and NT-proBNP similarly predicted all-cause mortality, while NT-proBNP outperformed BNP for the prediction of mortality and morbidity or hospitalization for HF (Masson et al. 2006). Moreover, experience from the Val-HeFT indicates that changes over time in natriuretic peptides, too, hold a prognostic value in stable HF, envisaging a role for serial BNP and NT-proBNP testing in patient monitoring and in the evaluation of response to therapeutical strategies (Masson et al. 2008; Richards 2008).

2.2   B-type Natriuretic Peptide-Guided Therapy

Circulating levels of B-type natriuretic peptides are influenced by most of the pharmacological and non-pharmacological therapeutical approaches in acute, acutely decompensated, and chronic HF. Indeed, in the acute setting, treatment with furosemide and the inodilator levosimendan decreases BNP (Cohen-Solal et al. 2009; Farmakis et al. 2010; Palazzuoli et al. 2014). Moreover, a reduction >30% from baseline values following levosimendan administration has been associated with an improvement in either short- (31 days) or long-term (180 days) mortality (Cohen-Solal et al. 2009). Other therapeutic strategies acting on hemodynamics and cardiac remodeling have been demonstrated to elicit similar effects on natriuretic peptides in stable HFrEF, including angiotensin-converting enzyme inhibitors (Rosenberg et al. 2008), angiotensin-receptor blockers (Anand et al. 2003), mineralocorticoid receptor antagonists (Berry et al. 2007), and, at a lower extent, β-blockers, whose initiation may also cause a transient increase in

BNP and NT-proBNP, which subsequently decrease (Davis et al. 2006; Rosenberg et al. 2008). Evidence for a beneficial effect on natriuretic peptides also exists for other non-pharmacological tools, such as aerobic training and cardiac resynchronization therapy (Fruhwald et al. 2007; Passino et al. 2006). More recently, the first-in-class neprilysin/angiotensin receptor inhibitor sacubitril valsartan (LCZ696) has been proved effective in reducing the risks of death and of hospitalization in patients with HFrEF compared to enalapril in the PARADIGM-HF trial (McMurray et al. 2014). Such beneficial effects are possibly due, at least in part, to the inhibition of BNP degradation exerted by sacubitril, while its precursor and NT-proBNP are virtually resistant to degradation (Semenov and Katrukha 2016), as also supported by the observation that after LCZ696 initiation, circulating levels of NT-proBNP decrease, while BNP slightly increases (Packer et al. 2015). It has been therefore questioned that assessing the clinical significance of BNP in the era of LCZ696 may be challenging and that NT-proBNP may be preferred over BNP for biochemical monitoring of patients with HF, in order to assess its effectiveness on hemodynamic status (Lippi and Sanchis-Gomar 2016).

As discussed before, natriuretic peptides perform well for diagnostic and prognostic purposes and are associated with disease severity and, importantly, their circulating levels change in response to evidence-based therapies for HF. Based on these premises, several studies have tested the (cost)effectiveness of strategies of treatment titration guided by natriuretic peptide circulating levels, the so-called *biomarker-guided therapy*. In the BATTLESCARED, the first of these studies, 364 HF patients were randomly allocated to therapy guided by NT-proBNP levels (with adjustments in medications and additional follow-up visits triggered by an NT-proBNP level >150 pmol/l) or by intensive clinical management, or according to usual care (Lainchbury et al. 2009). NT-proBNP-guided treatment was associated with a significant reduction in a primary end-point of death and/or readmission with heart failure in younger population (age ≤75 years), who also presented more often with HFrEF (61% vs. 47% in patients aged >75 years). In the same year results from the TIME-CHF trial, enrolling only patients with LVEF ≤45%, were published, showing that patients with therapy titration based on NT-proBNP (target: <400 ng/L in patients aged <75 years and <800 ng/L in patients ≥75 years) had improved 18-month survival free of hospitalizations for HF (Pfisterer et al. 2009). Following these pivotal trials, other studies using either BNP or NT-proBNP have provided mixed outcomes (Kim and Januzzi 2010). Some systematic reviews have addressed the issue of the effects on hard end-points, such as all-cause mortality, demonstrating a benefit from natriuretic peptide-guided therapy (Don-Wauchope and McKelvie 2015), and a meta-analysis by Felker has demonstrated a 30% improvement in survival, without an increase in therapy-related adverse events (Felker et al. 2009). As a general view, the use of natriuretic peptide to tailor HF therapy is likely to be more effective when lower target values are applied (i.e., <100 ng/L and <1,000 ng/L for BNP and NT-proBNP, respectively) (Januzzi et al. 2011; Jourdain et al. 2007; Troughton et al. 2000). Nonetheless, evidence is still scarce to support a general recommendation and some issues

still need to be addressed, including the most appropriate use of biomarker with this respect (disease management vs. monitoring), the choice of the end-point, and the cost-effectiveness of such a strategy (Pruett et al. 2015).

2.3 Back to the de Bold's "Atrial Natriuretic Factor": MR-proANP

Although B-type natriuretic peptides represent the most widely studied cardiac hormones, both in the experimental and clinical field, atrial natriuretic peptide (ANP) was first described in early 1980s, as a substance secreted from atrial granules with endocrine functions, by Adolfo de Bold (de Bold 1981). ANP assay has with time been substituted by assays of B-type natriuretic peptides both for analytical and clinical reasons (Clerico 2006). More recently, the potential clinical applications of the mid-regional pro-atrial natriuretic peptide (MR-proANP), with a longer half-life than ANP, have been tested. Data from the Biomarker in the Acute Heart Failure (BACH) and the PRIDE study have demonstrated a good performance of MR-proANP for diagnostic and prognostic purposes in acute HF, even in addition to NT-proBNP (Maisel et al. 2011a; b, c; Shah et al. 2012). MR-proANP also revealed a significant prognostic value in 1237 patients with chronic HF enrolled in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) study (proposed cutoff 278 pmol/L, AUC 0.74, 0.71–0.77), outperforming other established and candidate biomarkers (including copeptin and mid-regional proadrenomedullin, MR-proADM, and C-terminal proendothelin-1) and beyond NT-proBNP and a set of clinical variables (NRI = 0.06) (Masson et al. 2010a).

2.4 Cardiac Troponins

Cardiac troponins are released into the circulation following the disruption of cardiomyocyte membrane due to cardiac injury, namely after cardiac necrosis, and have become the standard of care biomarker for diagnosis of myocardial infarction. Nonetheless, elevation of circulating troponins has been reported also in non-acute settings, including chronic HF, due to mechanisms still to be fully elucidated, possibly involving inflammation, neurohormonal activation, myocardial stretch, hypoxia, and cytotoxicity (Gaggin and Januzzi 2013). With the improvement in troponin assays and the rise of high-sensitivity troponins (hsTn), detectable circulating troponin is now observed in a large proportion of HF patients and several studies have explored its use in clinical practice as an additional biomarker for disease management. In 140 patients with acute HF, TnI was found to be increased in about 1/3 of cases and to independently predict 90-day mortality and readmission. Further, increase in TnI during hospitalization was also associated with a worse outcome (Xue et al. 2011). In the RELAX-AHF trial, hs-TnT was elevated above the 99% upper reference limit in most of the AHF patients. Baseline, peak, and peak change hs-cTnT were associated with worse

outcomes, in particular with 180-day cardiovascular mortality (Felker et al. 2015). In the ADHERE study, patient with TnI elevation had significantly higher in-hospital mortality when treated with intravenous inotropic therapy as compared with intravenous vasodilator therapy (Peacock et al. 2008).

As in acute settings, circulating Tn is associated with prognosis also in chronic HF. In an analysis performed in >4000 patients enrolled in the Val-HeFT, TnT was detectable in about 10% of patients using a conventional assay, while 92% showed detectable Tn when the hsTnT assay was used. In the same cohort, hsTnT was associated with the risk of death and LV remodeling, and improved prognostic discrimination when added to a baseline model including BNP (Latini et al. 2007). The prognostic utility of serial Tn measurement in chronic HF has been investigated in patients from both the Val-HeFT and the GISSI-HF study. In this cohort, although increase in hsTnT over 3 to 4 months was strongly associated with all-cause mortality after adjustment for clinical risk factors, baseline levels, and NT-proBNP, it only modestly improved prognostic discrimination (Masson et al. 2012).

Previous reports show an association between the use of ACEi and beta-blockers with lower circulating Tn levels (Horwich et al. 2003; Masson et al. 2012), thus suggesting that guideline-recommended therapy may mitigate the risk in subsets with elevated Tn. More recently, in the PARADIGM-HF trial, treatment with LCZ696 led to a significant and sustained reduction in hsTnT that was not observed in the enalapril arm (Packer et al. 2015). Still, the issue of a Tn-guided therapy in chronic HF remains to be explored.

2.5 Candidate Biomarkers of HFrEF

Natriuretic peptides represent nowadays a fundamental aid to the clinical management of HF; nonetheless circulating levels of either BNP or NT-proBNP increase following each generic insult to the cardiovascular system. Therefore, while they are highly sensitive in the detection of ongoing damage, they are not able to provide clinically significant information concerning the nature of the *noxa*. The development and progression of the HF syndrome result from a complex interplay between different pathogenic determinants sustaining the ongoing myocardial damage and (mal)adaptive mechanisms. As a consequence, biomarkers providing insights into the extent of activation of specific axes of disease progression may help the clinician in the process of disease (and patient) characterization and of treatment tailoring.

A huge number of biomarkers have been tested or are currently under investigation for HF which may be classified according to he pathophysiological mechanism of damage they are considered to reflect. As previously suggested, biomarkers of sympathetic and RAAS activation, inflammation, fibrosis, and comorbidities can be distinguished (Braunwald 2013; Emdin et al. 2009).

2.5.1 Sympathetic Activation

Activation of the sympathetic, and inhibition of the parasympathetic system, represents one of the first (mal)adaptive mechanisms in disease onset and progression and one of the bases of the neuroendocrine model of HF, given its vasoconstrictive, profibrotic, and arrhythmogenic effects (Leimbach et al. 1986). Circulating norepinephrine increases with disease severity (Emdin et al. 2004), and, in a seminal paper by Cohn, it was the only independent predictor of mortality in 106 patients with moderate to severe HF, although such finding was not confirmed later on in more contemporary series (Cabassi et al. 2013; Cohn et al. 1984). Data from the Val-HeFT have shown that treatment with valsartan can blunt the increase in norepinephrine compared to placebo, while it was not affected by the mineralocorticoid receptor antagonist (MRA) spironolactone (Latini et al. 2002; Rousseau et al. 2002).

Together with catecholamines, chromogranin A is a component of chromaffin granules in the adrenal glands and, although its biological effects on the cardiovascular system remain to be elucidated, it seems to be involved in the regulation of adrenergic system (Tota et al. 2014). Limited evidence exists that circulating chromogranin A is increased in either acute or chronic HF and that may have some prognostic value (Dieplinger et al. 2009a; Røsjø et al. 2010).

2.5.2 Renin-Angiotensin-Aldosterone System Activation

RAAS is a complex endocrine system participated by the kidney, liver, vascular endothelium, and adrenal cortex regulating salt/water homeostasis and vasomotion. Either systemic or tissue RAAS are involved in tissue remodeling after damage, and can promote fibrosis, hypertrophy, and apoptosis. All the effectors of RAAS are increased in chronic HF (Emdin et al. 2004) and RAAS activation is an indirect or direct target of most effective pharmacological treatments in heart failure, such as beta-blockers, inhibitors of angiotensin-converting enzyme, angiotensin receptor blockers, direct renin inhibitors, mineralocorticoid receptor blockers, and angiotensin receptor/neprilysin inhibitors. Circulating biomarkers of RAAS activation are currently available, such as plasma renin activity (PRA), renin, angiotensin II, and aldosterone, although with different feasibility and accuracy, and some of them are well-recognized prognostic factors, even in patients with optimal therapy. Notably, chronic use of drugs acting on RAAS induces, per se, neurohormonal reactivation (Lee et al. 1999; Rousseau et al. 2002).

PRA has been demonstrated to hold an independent prognostic value in a systolic HF cohort on evidence-weighted treatment, with and without significant renal comorbidity (Poletti et al. 2013; Vergaro et al. 2011), thus potentially qualifying as a tool to identify patients with persistent RAAS activation despite adequate neurohormonal antagonism and to select subsets at higher risk for cardiovascular events. Further, aldosterone was shown to be a predictor of all-cause mortality in ≈300 patients with HF (most of them with systolic dysfunction), independently from other clinical and biohumoral variable including NT-proBNP (Güder et al. 2007). Specifically, the increase in circulating aldosterone following the initiation of RAAS acting therapy, a phenomenon termed "aldosterone

breakthrough," may hold clinical relevance, given the growing evidence on non-mineralocorticoid receptor-mediated effects of aldosterone. Further, in a small group of patients with systolic HF, increased PRA predicted ACE inhibitor-induced natriuresis (Lim et al. 2000).

The above-mentioned data support the rationale for the use of biomarkers of RAAS activation as a guide for treatment monitoring and tailoring, as well as a rule-in variable for trials in HF setting, a role up to now discarded as for the case of trials with the direct renin inhibitor aliskiren.

2.5.3 Inflammation and Immunity

There is growing information on the role of inflammatory cells and pathways during acute cardiovascular injury and in the reparative process that is subsequently activated. Elevation of inflammatory biomarkers, including C-reactive protein (CRP), members of the interleukin family (e.g., IL-1, IL-6, and IL-18), and TNF-α, is a hallmark feature of chronic ischemic and non-ischemic HF, although whether inflammation is causative to disease progression is not yet clear (Mann 2015). Moreover, viral infection is thought to participate in the development of dilated cardiomyopathy, sustaining acute and chronic inflammation (Kühl et al. 1996).

The Val-HeFT study demonstrated a direct correlation between elevated CRP level and HF severity (Anand et al. 2005); further, CRP predicts the risk of death and early readmission in acutely decompensated HF (Lourenço et al. 2010). Anti-inflammatory properties have been described for statins and their effect has been tested in HF settings. Data from the CORONA study show that subjects with HF of ischemic etiology and elevated baseline high sensitivity-CRP ($\geq$2 mg/L) exhibited a greater benefit from statin therapy in terms of reduction of the primary end-point of cardiovascular death, myocardial infarction, and stroke (McMurray et al. 2009), while controversial results come from studies performed on patients with HF of non-ischemic origin (Bleske et al. 2006; Sola et al. 2006).

Some trials have addressed TNF-α elevation in HF, which is associated with worsened prognosis. Two large clinical studies, the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) and the Research into Etanercept Cytokine Antagonism in Ventricular Dysfunction (RECOVER), were stopped because of lack of clinical benefit, and patients receiving the highest dose had increased adverse cardiac outcomes (Mann et al. 2004). Similar results were observed in the Anti-TNF-α in Congestive Heart Failure (ATTACH) trial, testing humanized neutralizing antibodies (infliximab) instead of the soluble receptor etanercept (Chung et al. 2003). The negative results of such trials may be, at least in part, explained by the inappropriate blockade of "physiological" inflammation that may be required for tissue-reparative processes.

2.5.4 Fibrosis

Galectin-3 In recent years galectin-3 (Gal-3), a soluble β-galactoside-binding lectin, has been found to play an important mechanistic role in the development

of cardiac fibrosis and remodeling and to identify high-risk subsets in HF cohorts, thus qualifying both as a risk marker and a risk factor (de Boer et al. 2009). There is a growing amount of evidence that Gal-3 is essential for migration and phagocytic activity of macrophages. Macrophage-derived Gal-3 may then act on fibroblast proliferation and on collagen synthesis, by increasing collagen I and reversing the collagen I-to-collagen III ratio (Henderson and Sethi 2009). Together with liver and kidney fibrosis, Gal-3 has been strictly linked to the development of cardiac fibrosis, a key determinant of cardiac remodeling and HF progression, possibly by interacting with mechanisms of aldosterone-mediated damage (Vergaro et al. 2016). Further, circulating levels of Gal-3 are associated with biomarkers of extracellular matrix turnover (including PIIINP, TIMP-1, and MMP-2), after adjustment for several clinical variables in a population 106 patients with systolic HF (Lin et al. 2009).

The experimental demonstration of a mechanistic involvement of Gal-3 in fibrotic, inflammatory, and remodeling processes in heart disease led to a novel interest in the potential use of Gal-3 assayed in plasma, as a biomarker. van Kimmenade and colleagues in 2006 first compared NT-proBNP, apelin, and Gal-3 in the management of acute HF patients (van Kimmenade et al. 2006). Out of 599 acutely dyspneic patients, 209 were later diagnosed with HF. Although Gal-3 showed a limited diagnostic accuracy in identifying acute HF, it was the strongest predictor of early events (60-day re-hospitalization for HF or all-cause mortality). Later on, Gal-3 was also demonstrated to predict long-term outcome (4-year mortality) in another cohort of acute HF patients (proposed cutoff: 14.97 ng/mL), independently of echocardiographic indices of cardiac structure and function (LV end-diastolic/systolic diameter, EF and right ventricular pressure) (Shah et al. 2010). In the following years the prognostic role of Gal-3 in HF settings has been investigated in some substudies from larger clinical trials. Gal-3 levels were determined in 232 NYHA III–IV chronic HF patients enrolled in the Deventer-Alkmaar HF (DEAL-HF) study, who were then followed up for a period of 6.5 years (Lok et al. 2010). Baseline Gal-3 (cutoff: 17.6 ng/ml) predicted all-cause mortality after adjustment for age, gender, creatinine clearance, and NT-proBNP. By dichotomizing the population according to NT-proBNP and Gal-3 levels, the authors also demonstrated an additive prognostic power for Gal-3, since patients with elevation of both biomarkers had a 1.5- to 2-fold higher mortality rate compared to patients in other subgroups. In a larger population of 895 chronic HF patients from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise TraiNing) study with LVEF <35%, Gal-3 lost its univariate prognostic value in predicting the composite outcome of all-cause death or re-hospitalization, when corrected for peak oxygen consumption at cardiopulmonary test or NT-proBNP (Felker et al. 2012).

Despite this wide amount of data confirming its prognostic role in HF, there is still limited information on whether Gal-3 assay may help in adjusting therapeutical strategies. Current knowledge is indeed limited to a benefit from statin therapy in patients with chronic HF of ischemic cause and low Gal-3 level (Gullestad et al.

2012) and to the lack of power in predicting response to mineralocorticoid receptor antagonists or to cardiac resynchronization therapy (Gandhi et al. 2015; Lopez-Andrès et al. 2012).

Recently, measurement of Gal-3 has received a class IIb recommendation in acute decompensated (level of evidence A) and in chronic (level of evidence B) HF for risk stratification purposes in the 2013 ACCF/AHA Guideline for the Management of Heart Failure (Yancy et al. 2013).

sST2 Suppression of tumorigenicity 2 protein (ST2) is a member of the Toll-like/ interleukin-1 receptor superfamily, which is expressed together with its ligand interleukin-33 (IL-33) following myocardial stretch and cardiovascular injury. The IL-33/ST2 interaction exerts positive effects in terms of blunting prohypertrophic and profibrotic signals (Kakkar and Lee 2008; Pascual-Figal and Januzzi 2015; Yancy et al. 2013). Indeed, the transmembrane receptor for IL-33 (ST2 ligand, ST2L) is one of ST2 isoforms. Among others, a soluble isoform of ST2 exists, sST2, arising from a dual-promoter system driving differential mRNA expression. There is evidence that sST2 may act as a decoy receptor competing with ST2L for IL-33 binding. For example, administration of IL-33 to cultured rat neonatal cardiomyocytes inhibited the prohypertrophic signals of angiotensin II or phenylephrine, these effects being reversed by sST2 (Sanada et al. 2007). Reflecting these experimental evidences, serum levels of sST2 have been associated to LV systolic function and remodeling, as well as to a more decompensated hemodynamic profile (Shah et al. 2009). Of interest, sST2 concentration does not appear to be influenced by age, kidney function, or body mass index, unlike natriuretic peptides (Dieplinger et al. 2009b).

sST2 assay has been tested for diagnostic and prognostic purposes in either acute or chronic HF populations. Data from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study have shown higher sST2 concentration in subjects with acute HF compared to those with dyspnea of non-cardiac origin (Januzzi et al. 2007). In the same cohort, sST2 was reported to be the best predictor of 1-year death, outperforming NT-proBNP (hazard ratios equal to 4.6 and 2.3, respectively) (Januzzi et al. 2010). Interestingly, in a population of acute HF patients, most of them with LV systolic dysfunction, sST2 provided additional prognostic value over NT-proBNP in the prediction of death, even in subset with lower NT-proBNP (Rehman et al. 2008). Fewer studies have explored the prognostic value of sST2 in chronic HF. In a well-treated subset of patients enrolled in the HF-ACTION trial, with LVEF <35%, ST2 was only modestly associated with functional capacity while it was significantly associated with outcomes (death or hospitalization, cardiovascular death or HF hospitalization, and all-cause mortality). In the larger study in chronic HF patients, a post hoc analysis of the Val-HeFT, baseline sST2 levels added significant information to the Cox regression model of first morbid events composed of 23 clinical variables including NT-proBNP and the treatment allocation (Anand et al. 2014). In the same study, sST2 values were also available at 4 and 12 months and patients randomized to the valsartan arm showed a

milder increase in sST2 over time compared to those assigned to placebo. Further, sST2 was the only circulating biomarker, in an analysis including also growth differentiation factor-15 (GDF-15) and hs-TnT to add prognostic information to baseline concentration and to predict the occurrence of reverse remodeling when serially tested in chronic systolic HF patients (Gaggin et al. 2014). Based on these data, and on the association of neurohormonal antagonism therapy with lower sST2 concentrations, sST2 is particularly promising as a tool for patient monitoring and therapeutic optimization (Januzzi et al. 2015). Further, as for Gal-3, sST2 measurement has received a class IIb recommendation in acute decompensated (level of evidence A) and in chronic (level of evidence B) HF for risk stratification purposes in the latest American guidelines (Yancy et al. 2013).

2.5.5 Cardiorenal Syndrome

Renal impairment and worsening renal function are very common in HF, and represent a key element in disease pathophysiology, thus constituting an aspect of the clinical spectrum of HF – configuring the so-called cardiorenal syndrome – rather than a mere comorbidity. In this view, the clinical utility of both markers of renal function and of renal damage has been tested in HF patients. Although kidney dysfunction generally reflects a loss of glomerular filtration rate (GFR), it is participated by alteration in renal hemodynamics, sodium and water retention, and glomerular and tubulo-interstitial function. Biomarkers have been proposed (and tested) in HF settings to investigate each of these aspects.

Chronic kidney disease, as assessed by either GFR or serum creatinine, is strongly associated with a worse outcome in HF patients (Dries et al. 2000; Hillege et al. 2000). Worsening renal function is also frequent in HF, sometimes associated with the initiation of RAAS-acting therapy. This phenomenon, termed "pseudo-worsening renal function," is likely to have scarce effects on prognosis and may be associated with beneficial effects of ACE inhibitors in patients with LV systolic dysfunction (Clark et al. 2014; van Veldhuisen et al. 2015). Cystatin C is a small (13 kDa) protein produced by all nucleated cells, filtered and then catabolized by tubular cells, that can be considered an alternative tool to estimate renal function. A prognostic value has been demonstrated for cystatin C in chronic HF population (Damman et al. 2012) but it has never been used as a guide for HF treatment yet.

Albuminuria and proteinuria both reflect loss of integrity and damage to the glomerular membrane. Analyses from >2000 patients with chronic HF enrolled in the GISSI-HF study have shown an increasing mortality rate in subjects with normal albumin excretion, microalbuminuria or albuminuria, even after adjustment for other clinical risk factors (Masson et al. 2010b), with additive prognostic properties over GFR (Damman et al. 2011).

Some markers of tubular damage, including neutrophil-gelatinase-associated lipocalin (NGAL), kidney injury molecule (KIM)-1, and N-acetyl β-(d)-glucosaminidase (NAG), have been used for (early) detection of acute kidney injury. NGAL is a siderophore-binding protein expressed by various epithelial cells which is over-expressed in kidney injury and can be dosed in either serum or urine. Serum NGAL may be of help for prediction of acute kidney injury and in

risk stratification in acute HF (Aghel et al. 2010; Maisel et al. 2011b). In patients
with chronic HFrEF enrolled in the CORONA study, plasma NGAL did not add
significant prognostic information when included in a model with NT-proBNP and
GFR (Nymo et al. 2012). Also KIM-1 and NAG are increased in chronic HFrEF and
may provide clinical aid in the prediction of worsening renal function in HF, while
solid evidences on their prognostic value are still lacking (Jungbauer et al. 2011).

2.5.6 Comorbidities and Cachexia

HF is a systemic syndrome and peripheral organ dysfunction may either contribute
to the disease onset and progression or represent a consequence of primitive cardiac
abnormalities.

Thyroid hormones are crucial for cardiovascular homeostasis and even subclini-
cal alteration of thyroid function is associated with worsened outcome in HF
patients, independently from natriuretic peptides (Passino et al. 2009).
Low-triiodothyronine syndrome is a recognized entity in HFrEF but, despite
some promising results from animal studies and small-scale supplementation trials,
general recommendation is still lacking (Gerdes and Iervasi 2010). Among hema-
tologic conditions, anemia is prevalent in acute and chronic HF and low hemoglo-
bin levels hold significant prognostic value, additive to NT-proBNP (Baggish et al.
2007). Further, ferritin and transferrin saturation assessment is of key importance to
identify subgroups of patients with iron deficiency, which is coming up as a
therapeutical target in patients with HFrEF, as confirmed in a recent meta-analysis
(Qian et al. 2016).

Cachexia and wasting frequently develop in later stages of HF, as a consequence
of a complex interplay among (neuro)hormonal, immune, inflammatory
dysregulation and anabolic/catabolic imbalance. Ghrelin and adiponectin are pep-
tide hormones involved in energy balance, and are both increased in cachectic
chronic HF patients. Some evidence exists that adiponectin predicts mortality in
systolic HF and that treatment with the beta-blocker carvedilol decreases
circulating levels of adiponectin (Tsutamoto et al. 2007; Yamaji et al. 2009).

2.5.7 Adrenomedullin

Adrenomedullin (ADM) is a peptide hormone acting as a potent vasodilator
expressed by all human tissues. Circulating ADM is increased in HF and correlates
with disease severity. Nonetheless, ADM is highly unstable and, recently, a novel
assay measuring the mid-region of the more stable prohormone (MR-proADM) has
been developed, with similar behavior in HF patients (Shah et al. 2012). Prognostic
value of ADM has been tested in a cohort of 297 patients with HFrEF of ischemic
origin. In this study ADM predicted the risk of mortality and of HF hospitalization
independently from other clinical variables (Richards et al. 2001). Interestingly, an
interaction with carvedilol therapy was reported in the same paper.

2.5.8 GDF-15

Growth differentiation factor 15 (GDF15) is a member of the TGF-ß cytokine
superfamily which is highly expressed during inflammatory stress. GDF circulating

levels are increased in HF patients and correlate with the extent of myocardial fibrosis (Lok et al. 2012). Both baseline and repeated measurements of GDF-15 have additional prognostic value over hsTnT and NT-proBNP in patients with HFrEF (Chan et al. 2016). In an analysis from the Val-HeFT study, an independent, although weak, predictive value of GDF-15 for all-cause mortality was also shown, with GDF-15 levels increasing over time independently from the assignment to the placebo or the valsartan arm (Anand et al. 2010).

2.5.9   Copeptin

Arginine vasopressin (AVP), also known as antidiuretic hormone, is involved in the regulation of free water clearance, plasma osmolality, and vasomotricity. It is known since a long time that circulating AVP is elevated in HF settings (Goldsmith et al. 1983), but its assay is challenging. Copeptin, the c-terminal segment of the precursor of provasopressin, is a reliable surrogate marker for AVP and has been proved to independently predict mortality in acute HF, especially in subsets with hyponatremia (Maisel et al. 2011c). In 195 patients with chronic HFrEF, copeptin predicted 5-year all-cause mortality, although with poor additive prognostic accuracy over NT-proBNP (IDI 9.3%, NRI 8.2%) (Pozsonyi et al. 2015).

2.5.10   miRNAs

MicroRNAs (miRNAs) are non-coding RNAs which are involved in different cell processes by repressing messenger RNA translation. miRNAs have been shown to participate in several pathophysiological processes related to heart failure, including cardiac fibrosis and hypertrophy. Several circulating miRNAs have been tested for diagnostic and prognostic purposes either in acute or in chronic HF (Vegter et al. 2016). For example, Tijsen has reported that miR-423-5p is differentially expressed between HF patients, healthy controls, and patients with dyspnea of non-cardiac origin (Tijsen et al. 2010). In a small cohort of patients with chronic HF, miR-126 and miR-508-5p are associated with cardiovascular death in subsets with ischemic and non-ischemic HF, respectively (Qiang et al. 2013). Interestingly, there is experimental evidence that circulating miRNAs fluctuate in response to pharmacological HF treatment (e.g., by ACE inhibitors) and that miRNAs may represent, themselves, a therapeutical target (Vegter et al. 2016).

3   Biomarkers of Heart Failure with Mid-Range and Preserved Ejection Fraction

Among HF patients, a significant proportion exists presenting with preserved or only slightly impaired EF, especially in the elderly population. As mentioned above, these clinical entities have been defined as HFpEF and as HFmrEF in the latest European guidelines for the management of acute and chronic HF. Although specific EF cutoff has been proposed in these recommendations, in previous studies different definitions of "preserved" EF have been considered, ranging from 40 to

55%. There is therefore consistent overlap among HFpEF and HFmrEF; thus we will consider them on a whole in the following section.

Independent from its definition, HFpEF is associated with high rates of morbidity and mortality both in ambulatory and in-hospital settings, comparable to HFrEF (Senni et al. 2014). Nonetheless, while in the last few decades, several pharmacological and non-pharmacological approaches have been validated for HFrEF, up to now no single intervention has been demonstrated to modify the clinical course of HFpEF, possibly due to a consistent phenotypic variability and to the enrolment of heterogeneous population in large clinical trials (Butler et al. 2014). Different pathophysiological mechanisms indeed underlie the development of the clinical syndrome of HFpEF and the role of comorbidities is likely more relevant than in HFrEF. In the effort toward individualization that is therefore required for the management of HFpEF, circulating biomarkers – tracking specific damage pathways – may represent fundamental tools.

3.1   Natriuretic Peptides

As discussed above, natriuretic peptides are the cornerstone biomarkers in HFrEF. Nonetheless, their clinical value has been demonstrated across the whole spectrum of LV systolic function. Although to a lower extent as compared to patients with more severe reduction in EF, both BNP and NT-proBNP are increased and are key elements in the diagnosis of HFpEF. Moreover, their levels increase with more severe cardiac morphological and functional abnormalities (including hypertrophy, fibrosis, and diastolic dysfunction) (Tschope et al. 2005). Still, a clear cutoff does not exist to distinguish HFpEF from HFrEF (Parekh and Maisel 2009; van Veldhuisen et al. 2013). Further, prognostic properties of BNP are maintained independently from the extent of LV dysfunction, since, for a given BNP level, the risk of death and HF hospitalization of patients with HFpEF is as poor as in those with reduced LVEF (van Veldhuisen et al. 2013). The prognostic value of NT-proBNP has also emerged in HFpEF patients (defined as LVEF $\geq$45%) from the i-PRESERVE study, showing that baseline (proposed cutoff 339 pg/mL) and changes in NT-proBNP improve the prediction of mortality and HF re-hospitalization (Anand et al. 2011; Jhund et al. 2015).

As for the case of HFrEF, circulating levels of natriuretic peptides are influenced by several cardiac and extra-cardiac conditions (including female sex and advanced age), which is even more important in HFpEF, given the high prevalence of comorbidities. For example, a fivefold increase in NT-proBNP has been reported in subjects with HFpEF and atrial fibrillation, compared to those in sinus rhythm (McKelvie et al. 2010); likewise, renal function has been reported to significantly influence natriuretic peptide concentration (McCullough et al. 2003).

A few studies have specifically explored the effectiveness of a natriuretic peptide-guided therapy in HFpEF. Maeder and colleagues enrolled 123 patients with HF and LVEF >45%, who were randomized to medical therapy titrated to reduce symptoms to NYHA $\leq$ II or also to reduce NT-proBNP below the inclusion

threshold (>400 or >800 ng/L depending on age). Differently from patients with HFrEF, NT-proBNP-guided management tended to worsen 18-month outcomes in HFpEF (Maeder et al. 2013), thus questioning the clinical benefit of such approach, as later confirmed in a recent individual patient meta-analysis (Brunner-La Rocca et al. 2015).

3.2   Other Biomarkers in HFpEF

As mentioned before, HFrEF and HFpEF are likely sustained by a different pathophysiology, thus explaining the variable response to pharmacological and non-pharmacological treatment. Analyses of data from the Trial of Intensified versus standard medical therapy in elderly patients with congestive heart failure (TIME-CHF) have shown a different circulating biomarker profile in patients with LVEF $\leq 40\%$ ($n = 458$) vs. those with LVEF $\geq 50\%$ ($n = 112$). After adjustment for other clinical variables accounting for heterogeneity between populations, patients with HFpEF displayed significantly higher levels of sST2, hs-CRP, and cystatin-C. On the other hand, HFrEF patients presented higher NT-proBNP, hs-TnT, and hemoglobin (Sanders-van Wijk et al. 2015). These results suggest that markers of myocardial damage and loading are activated in HFrEF, while elevation of biomarkers of inflammation and fibrosis characterizes HFpEF.

3.2.1   sST2
Among markers of inflammation and fibrosis, sST2 seems to be promising in the clinical management of HFpEF. First data came from a prognostic study showing that sST2, although not correlating with echocardiographic indices of diastolic function, was the only biohumoral marker predicting mortality in 200 patients with dyspnea and normal LV systolic function (Shah et al. 2011). These data have been confirmed in further studies, demonstrating that prognostic value of sST2 in HFpEF was comparable to that in HFrEF, especially in acute settings (Manzano-Fernández et al. 2011).

3.2.2   Gal-3
Gal-3 has also been mechanistically involved in the proceses of cardiovascular inflammation and fibroblast proliferation and fibrosis, which are thought to be at play in the development of HFpEF. In 2011 de Boer has shown that in HFpEF patients from the Coordinating study evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) (with LVEF $>40\%$), Gal-3 appeared to have a particularly strong predictive value, compared to HFrEF patients (de Boer et al. 2011). Gal-3 also yielded significant reclassification indices in one of the largest biomarker studies in HFpEF so far, conducted in a cohort of 419 HF patients with LVEF $>45\%$ (Carrasco-Sánchez et al. 2013). The Aldo-DHF trial explored the effects of spironolactone 25 mg vs. placebo in chronic HFpEF patients. Gal-3 was associated with functional performance and quality of life, and its increase in serial measurements predicted all-cause death or hospitalization independently from

NT-proBNP. However, no specific interaction between treatment arm and Gal-3 levels could be observed (Edelmann et al. 2015).

3.2.3 GDF-15

As previously discussed, GDF-15 is a marker of cell injury and inflammation that has been shown to circulate in higher concentrations in patients with HFpEF compared to controls (Stahrenberg et al. 2010). Diagnostic and prognostic properties have been advocated for GDF-15 in HFpEF. For example, the NT-proBNP/GDF-15 ratio has been shown to properly distinguish between HFpEF and HFrEF (AUC 0.709) (Santhanakrishnan et al. 2012); further, higher GDF-15 is associated with increased risk of death and HF hospitalization in HFpEF patients, providing additional prognostic information over hsTnT and NT-proBNP (Chan et al. 2016). Although not conclusive, these data strongly support a putative role of GDF-15 – both a determinant and marker of risk – as a useful tool for HFpEF management, as well as a possible therapeutical target (Putko et al. 2014a, b).

3.2.4 Inflammatory Biomarkers

Activation of pro-inflammatory pathways is a fundamental element in HFpEF pathophysiology (Paulus 2000). Elevated levels of inflammatory cytokines, such as TNF-α, IL1, IL6, IL8, and CRP, are often observed in HFpEF patient; interestingly, circulating levels of TNF-α receptors (TNFR1 and TNFR2) are associated with the severity of diastolic dysfunction and of symptoms (Putko et al. 2014a, b). Still, scarce evidence on their prognostic role is currently available.

3.2.5 Directions

Other biomarkers have been tested for the management of HFpEF in the past years, yielding different (in some case promising) results. For example, ADM levels have been correlated to diastolic dysfunction (Yu et al. 2001), and MR-proADM, which is also emerging in HFrEF, may help in identifying new-onset HFpEF (Brouwers et al. 2014). Von Willebrand factor has been shown to additive prognostic value over NT-proBNP in 457 patients with HFpEF enrolled in the LUdwigshafen Risk and Cardiovascular Health (LURIC) study (Kleber et al. 2015). In a small study, no significant difference in microRNA levels was identified between HFrEF and HFpEF.

RAAS activation is associated with most of the pathophysiological mechanisms leading to cardiac phenotypes commonly observed in HFpEF, including hypertrophy, apoptosis, and fibrosis; therefore, from a theoretical standpoint, biomarkers of RAAS should provide useful information for disease management and, possibly, for therapeutic optimization. Two trials, Aldo-DHF and TOPCAT, have investigated the effects of spironolactone in HFpEF patients showing no significant effect on outcome, despite a beneficial effect on diastolic function (Edelmann et al. 2013; Pitt et al. 2014). Also LCZ696 has been demonstrated to reduce left atrial volume in HFpEF (Solomon et al. 2012), but its prognostic effect is still under investigation in the phase III PARAGON-HF trial.

4   Conclusions

BNP and NT-proBNP have first demonstrated how biomarkers can dramatically influence the everyday management of HF patients, providing information to the clinician far exceeding initial expectations. Despite recent advances, HF still remains a syndrome with unacceptable morbidity and mortality, possibly reflecting a complex pathophysiology and an extremely heterogeneous presentation which is only partly counterbalanced by a "one-size-fits-all" therapeutic strategy. Novel biomarkers addressing specific disease phenotypes and paths of damage will be of help for treatment tailoring and to move toward a more rational use of drugs and devices in HF. Research has recently focused on the clinical value of Gal-3 and sST2, which are both markers and effectors of cardiovascular damage, but currently, still there is no clear indication for therapeutic driving or optimization based on circulating levels of such biomarkers and, more generally, on a single HF biomarker.

For prognostic purposes, it seems reasonable that the use of multiple markers reflecting the activation of different pathophysiological pathways may more accurately identify high-risk subjects. This hypothesis has been recently tested, for example, in a large cohort of decompensated HF patients who were tested for several (novel) HF biomarkers. Elevation of at least three among MR-proADM, hs-TnT, combined free light chains, hsCRP, and sST2 provided incremental prognostic value when added to a multivariable model including BNP (NRI 32.5%) (Jackson et al. 2016). Nonetheless, the feasibility and the cost-effectiveness of multimarker strategies remain to be elucidated.

During the last years, a growing number of biomarkers have been proposed as potentially useful in HF patients, but no one of them still resembles the characteristics of the "ideal biomarker." A single marker will hardly perform for screening, diagnostic, prognostic, and therapeutic management purposes; therefore, a rational use of biomarkers will likely contemplate different analytes for different purposes. Moreover, the pathophysiological and clinical significance of biomarkers may depend on the presentation, stage, and severity of the disease (e.g., on etiology, presence/extent of LV systolic dysfunction, comorbidities). In this view, one could envisage specific sets of biomarker with different performances in HFpEF, HFmrEF, and HFrEF, especially as concerns prediction of the future course of the disease and of LV adverse/reverse remodeling.

Biomarkers are likely the most promising tools to make a step toward individualized therapy in HF. In the next future, a lot will depend on the quality (even more than on results) of clinical studies aimed at improving current diagnostic and prediction models and of studies using biomarkers to tailor therapeutics.

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