Biomarker-Guided Therapy for Chronic Heart Failure

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Alexander E. Berezin

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Abstract

The interest in guided therapy for acutely decompensated and chronic heart failure using several biological markers, which vary according to the pathogenesis of cardiac failure, has been steadily increasing. The circulating levels of brain natriuretic peptide (BNP) and N-terminal prohormone of BNP (NT-pro-BNP) are routinely used in clinical practice to stratify the risk of patients with symptomatic chronic heart failure. This chapter discusses the goal of lowering concentrations of these markers and their continued suppression in the follow-up period as part of the current therapeutic approach to chronic heart failure. Although a recent

A.E. Berezin (✉)
Department of Internal Medicine, State Medical University of Zaporozhye, Zaporozhye, Ukraine
e-mail: dr_berezin@mail.ru; aeberezin@gmail.com

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European Society of Cardiology (ESC) guideline did not recommend biomarker-guided therapy based on BNP/NT-pro-BNP in the management of chronic heart failure patients, the American Heart Association/American College of Cardiology (AHA/ACC) clinical practice guidelines for heart failure have issued a class I and A-level of evidence for BNP/NT-pro-BNP, citing them as powerful tools to supplement clinical judgment in chronic heart failure management. However, this approach should aim for individualization of the treatment strategy. Likewise, several conceptual, methodological, and practical limitations of natriuretic peptide-guided therapy conflict with the contemporary strategic approach based on symptoms and echo-guided treatment of chronic heart failure. The clinically significant biological variability of natriuretic peptides result in a lower specificity than expected, higher cost, and slow time-course. In addition, the lack of conclusive scientific evidence over a long-term period of intensive scientific investigations and industry investment may indicate a need for new biological markers or novel combinations for multimarker predictive scores and guided therapy. The chapter considers the potency and clinical advantages of a novel strategic approach for CHF treatment based on serial measurements of biomarkers and creating optimal combinations of biological indicators with an aim to improve clinical outcomes, quality of life, and well-being for patients with cardiac failure.

Keywords

Biomarker-guided therapy, chronic heart failure • Biomarkers • Heart failure • Chronic heart failure • Biomarker-guided therapy • BNP-guided therapy • Brain natriuretic peptide (BNP) • Cost-effectiveness • Definition • Diagnosis and prognosis • Limitations • Natriuretic peptide-guided therapy • Novel biomarkers • Treatment strategy • Clinical endpoints • Serial measurements • Surrogate endpoints

Abbreviations

ACC	American College of Cardiology
ACEI	Angiotensin-converting enzyme inhibitors
ACS	Acute coronary syndrome
ADCHF	Acutely decompensated chronic heart failure
ADHF	Acutely decompensated heart failure
AHA	American Heart Association
ANP	Atrial natriuretic peptide
ARB	Angiotensin receptor blocker
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass grafting
CHF	Chronic heart failure
COPD	Chronic obstructive pulmonary disease
ESC	European Society of Cardiology
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
PCI	Percutaneous coronary intervention

Definitions

Biological marker-guided therapy of heart failure Achieving the optimal goals of heart failure patients based on a dose-adjusted approach of concomitant medications or use of new procedures and interventions under the control of serial measurements of biological markers.

Biomarker A biomarker is defined as an objectively measured indicator of several biological or pathological processes, pharmacologic responses, and therapeutic interventions that may have diagnostic and predictive values to use these markers as potent surrogate endpoint indicators.

Clinically based heart failure treatment In this traditional approach, the initial choice of drugs, optimal combinations and dosage regimen of remedies, and other procedures and interventions for heart failure are based on the analysis of appropriate signs, symptoms, and clinical response after prescribing.

Echo-guided heart failure management This treatment strategy of heart failure is based on serial measurements of echocardiographic parameters reflected in the global pump and diastolic function to correct the dosing of concomitant medications that are suitable for heart failure treatment.

Hemodynamically guided therapy of heart failure This treatment of heart failure is performed under the control of hemodynamics. Usually, this term is synonymous with echo-guided heart failure management.

Relevance Relevance is the ability of a biomarker to clarify clinically relevant of information that is important for healthcare professionals, public and health policy officials, physicians, and all other stakeholders.

Surrogate endpoint biomarker A surrogate endpoint biomarker is defined as an indicator of clear clinical endpoints in target patient populations only.

Validity Validity is defined as the need of a biomarker to exactly reflect the efficacy and/or utility as a surrogate endpoint.

Introduction

Chronic heart failure is the leading cause of cardiovascular morbidity and mortality worldwide (Santulli 2013). CHF occurs in 1–2 % of the adult population in developed countries; this rate rises to more than 10 % in individuals older than 70 years (Mosterd and Hoes 2007). A timely diagnosis and modern treatment can significantly improve both the short-term and long-term prognosis of this disease (Komajda et al. 2015). However, the expected 5-year survival of the patients after

a first admission for symptomatic chronic heart failure remains low and comparable with cancer, despite all of the advances in modern medicine (Stewart et al. 2001). Even patients who receive optimal chronic heart failure therapy may still experience acutely decompensated chronic heart failure, sudden cardiac death, fatal arrhythmias, and urgent admission due to chronic heart failure or other cardiovascular reasons (Schou et al. 2013). The understanding of chronic heart failure has progressed from the concept of a purely hemodynamic disorder to that of a syndrome resulting from dysfunction in several molecular pathways with mutual interconnections (Liu and Eisen 2014). As a result, the focus of research investigations and clinical care has shifted to the measurement and modification of maladaptive molecular processes (Ahmad and O'Connor 2013). In this regard, significant efforts to identify biological markers that reflect several biochemical processes and the risk of clinical outcomes in CHF patients have been used (Scali et al. 2014; Stienen et al. 2014).

Biomarker Definition

Biomarkers are objectively measured and evaluated as indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (Biomarkers Definitions Working Group 2001). Biomarkers may unmask different biological processes that contribute to several innate mechanisms of pathogenesis in heart failure and mediate a patient's response to treatment or procedures (Wang et al. 2012; Vasan 2006). Therefore, some biomarkers are considered to be surrogate end-points with high potency for utilization in the management of primary-care subjects and patients at discharge after acute or acutely decompensated heart failure (Bishu et al. 2012; Braun et al. 2009). An ideal biomarker is precise, accurate, and rapidly available to physicians without equivocal and controversial interpretation (Table 1); it should produce new or additional important information that cannot be surmised from clinical evaluation and may help in decision making, in addition to being low cost (Morrow and de Lemos 2007).

Table 1 Expected requirements for ideal biomarkers

Highly sensitive and specific
Easy to detect with low biological variation
Capable of reflecting appropriate molecular interaction, as well as functional, physiological, and biochemical processes at the cellular level
Capable of indicating an acute response after the drug is given or after injury
Quantitatively describes the level of injury by serial measurements
Closely correlates with the severity of disease and prognosis
Predicts progression and target-organ damage
Probability of risk stratification for new events and readmission
Low cost

The Natriuretic Peptides and Heart Failure

Atrial natriuretic peptide (ANP) and brain (or B-type) natriuretic peptide (BNP) are neurohormones secreted predominantly from cardiomyocytes in response to atrial or ventricular wall stretch and intracardiac volume loading (Ancona et al. 2007). The natriuretic peptides have a fundamental role in cardiovascular remodeling, volume homeostasis, and the response to myocardial injury. BNP is considered to be a counterregulatory hormone to angiotensin II, norepinephrine, and endothelin, having vasodilatorary and diuretic effects (Tsutamoto and Horie 2004). The precursor of BNP is pro-BNP, stored in secretory granules in myocytes. Pro-BNP is split by a protease enzyme into BNP and N-terminal pro-BNP (NT-pro-BNP) (Chen and Burnett 2000). BNP can be easily measured in plasma. The main causes of circulating natriuretic peptide elevation are listed in Table 2. The compensatory activity of the cardiac natriuretic peptide system may be attenuated as mortality increases in chronic chronic heart failure patients with high plasma levels of ANP and BNP (Mant et al. 2008). However, BNP and NT-pro-BNP are more useful than ANP for the diagnosis and management of acute decompensated chronic heart failure (Worster et al. 2008). Among patients with chronic heart failure, concentrations of natriuretic peptides are strongly linked to the presence and severity of structural heart disease and are strongly prognostic in this setting (Nishikimi 2012; Valle et al. 2008). Therefore, an average of BNP and NT-proBNP assay results may relate to structure remodeling and biomechanical stress of heart (Ohtani et al. 2012). Because patients with chronic heart failure and preserved left ventricular ejection fraction (LVEF) usually have

Table 2 The main causes of circulating natriuretic peptide elevation

Cardiac reasons	Noncardiac reasons
Heart failure (acute, acutely decompensated, chronic)	Age > 60 years
ACS/MI	Anemia
Stable CAD	COPD
Ventricular hypertrophy	Renal failure
Cardiomyopathies	Obstructive sleep apnea
Myocarditis	Pulmonary hypertension
Valvular heart diseases	Pulmonary thromboembolism
Pericardial disease	Pneumonia
Atrial fibrillation/flatter	Injury
Cardioversion	Malignancy
Cardiac surgical procedure, including PCI, CABG, and pacemaker implantation	Critical illness
Drug-induced cardiac toxicity (adriamycin, 5-ftoruracil)	Toxic-metabolic insult
	Sepsis
	Burns

ACS acute coronary syndrome, *MI* myocardial infarction, *PCI* Percutaneous Coronary Intervention, *CABG* coronary artery bypass graftingm, *COPD* chronic obstructive pulmonary disease, *CAD* coronary artery disease

Table 3 2013 ACC/AHA clinical practice guideline for heart failure: novel issues for biomarkers in heart failure management

Biomarkers	Target	Patient populations	Class of recommendation	Level of evidences
Natriuretic peptides	To establish or refute heart failure	All patients suspected of having HF, especially when the diagnosis is not certain	I	A
	Predict outcome	Outpatients with HF	I	A
	Guided-based therapy	Outpatients with HF	II a	B
	Diagnostic aim	Inpatients suspected with acute HF	II b	C
Cardiac specific troponins	Stratify at risk	Outpatients with HF	I	A
	Predict outcome	Inpatients suspected with acute, acutely decompensated or chronic ischemic HF		
Galectin-3	Stratify at risk	Outpatients with HF	II b	B
	Predict outcome	Inpatients suspected with acute HF	II b	A

HF heart failure

smaller LV cavities and thicker LV walls when compared with subjects with reduced LVEF, the intensity of biomechanical stress is also lower (Patel et al. 2014). It should be considered that patients with preserved LVEF are more likely to be older and female with obesity and hypertension than heart failure patients with reduced LVEF (Lund et al. 2014; Luchner et al. 2013; Mason et al. 2013). As a result, the circulation level of BNP/NT-proBNP may be detected in lower concentrations than in heart failure subjects with reduced LVEF (Tate et al. 2014). Moreover, heart failure patients with preserved LVEF may be more likely to have undetected circulating levels of BNP/NT-proBNP compared with persons without heart failure (Ohtani et al. 2012).

The current guidelines for chronic heart failure management indicate that evidence supports the use of natriuretic peptides for the diagnosis, staging, hospitalization and/or discharge decisions (Table 3), and identification of patients at risk for clinical events and readmission (Yancy et al. 2013; McMurray et al. 2012). Because about 50 % of individuals with left ventricular systolic dysfunction are asymptomatic, BNP levels have been evaluated for this purpose (Costello-Boerrigter et al. 2006; Wang et al. 2004). Currently, the measurement of plasma concentrations of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) is useful to rule out the diagnosis and to predict the prognosis of patients with ischemic and non-ischemic CHF (Table 4), although it remains unclear whether BNP-guided chronic heart failure therapy is beneficial and economically feasible (Vavuranakis et al. 2012). Clinical utilization of cardiac biomarkers in heart failure is reported in Table 5.

Table 4 Advantages and disadvantages of BNP/NT-proBNP implementation in routine clinical practice

Advantages	Disadvantages
More accurate differential diagnosis of acute dyspnea	High biological variability
Reflects the stage and prognosis of HF	No optimal cut-off points for patients older than 60 years
Easy and reproducible detection	Impossible to differentiate diastolic and systolic types of cardiac dysfunction
Ability to be detected by self-measurement	Underdiagnosed in patients with diastolic dysfunction
Low cost	A drop of 15 % and less within 5–7 days of admission due to acute or acutely decompensated heart failure requires additional consideration of the treatment response

HF heart failure, *BNP* brain natriuretic peptide

Table 5 Clinical utilization of cardiac biomarkers in heart failure

Natriuretic peptides[a]	BNP/NT-proBNP, midregional proBNP, midregional proANP
Cardiac injury biomarkers	Troponin T[a], troponin I[a], fatty acid binding protein
Metabolic markers	Adiponectin, grelin, apelin, leptin, insulin-like growth factor-1, cardiotrophin
Neurohormones	Catecholamines, renin, aldosterone, angiotensin, C-terminal pro-vasopressin, mid-regional pro-adrenomedullin, endothelin, urocortin, urotensin
Proinflammatory biomarkers	hs-CRP, galectin-3[a], TNF-alpha, ST2 protein[a], solubilized ST2 protein receptor, interleukins, Fas (APO-1), myeloperoxidase
Bone-related proteins	Ospeoprotegerin, osteopontin, osteonectin
Renal injury biomarkers	Creatinine, NGAL, cystatin C, KIM-1, L-FABP, cysteine-rich protein
Anemia biomarkers	Hemoglobin, RDW, transferrin, ferritin
Other biomarkers	Myotrophin, mRNA, growth differential factor-15, collagen peptides, matrix metalloproteinases, tissue inhibitors of matrix metalloproteinases, circulating endothelial-derived apoptotic microparticles, circulating mononuclear progenitor cells

hs-CRP high sensitive C-reactive protein, *mRNA* micro ribonucleic acid, *TNF* tumor necrosis factor, *APO-1* apoptosis antigen-1, *RDW* red cell distribution width, *NGAL* neutrophil gelatinase-associated lipocalin, *KIM-1* kidney injury molecule-1, *L-FABP* liver-type fatty acid binding protein
[a]Incorporated in clinical practice guidelines

The Principles of Natriuretic Peptide-Guided Therapy in Chronic Heart Failure

Standard chronic heart failure care may substantially improve outcomes in patients affected by the disorder. Unfortunately, the physical signs and symptoms of heart failure lack diagnostic sensitivity and specificity, and medication doses proven to

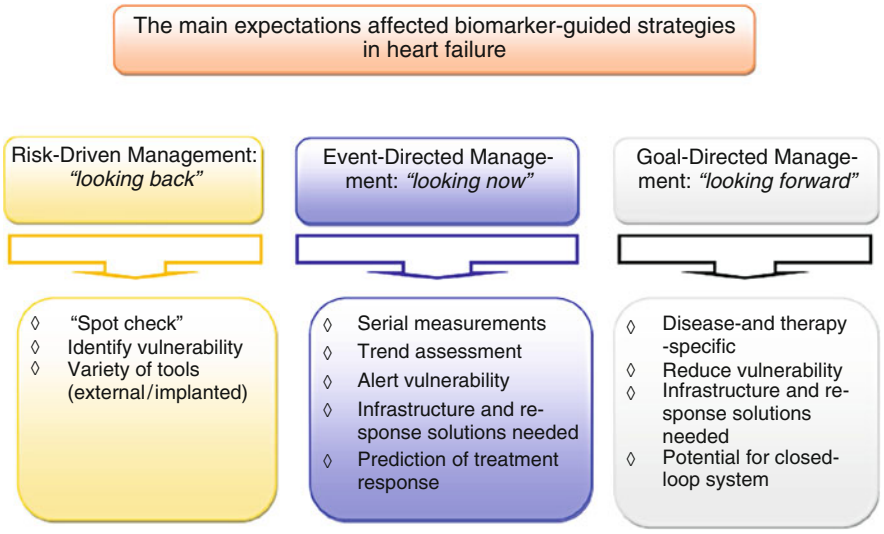

Fig. 1 The main expectations of biomarker-guided strategies in heart failure. This figure shows the principles of biomarker-guided therapy in heart failure that are considered to be suitable for achieving beneficial results (Adapted from data produced by Samara and Tang (2011))

improve mortality in clinical trials are often not achieved (Saremi et al. 2012). Biomarker-guided strategies for heart failure may have some advantages that are usually absent in symptom-based treatment approaches and echo-based strategies (Fig. 1).

Natriuretic peptide-guided chronic heart failure therapy has been given a recommendation in US chronic heart failure guidelines to achieve guideline-directed medical therapy (Class IIa) and possibly improve outcomes (Class IIb). Other clinical practice guidelines (including those from the European Society of Cardiology) are awaiting results from emerging clinical trial data (Yancy et al. 2013; McMurray et al. 2012). Biomarker-guided chronic heart failure trials indicate that the approach improves the quality of care without an excess of adverse events related to more aggressive management (Adams et al. 2010). Additionally, a favorable reduction in the concentration of BNP and NT-pro-BNP may be seen during treatment of chronic heart failure, with parallel improvement in short- and long-term prognosis. Given these issues, there is increasing interest in harnessing cardiovascular biomarkers for clinical applications to more effectively guide diagnosis, risk stratification, and further therapy (Fiuzat et al. 2013). The evidence for their use in monitoring and adjusting drug therapy is less clearly established (Vavuranakis et al. 2012). It may be possible to realize an era of personalized medicine for chronic heart failure care in which therapy is optimized and costs are controlled and, probably, reduced (Ahmad and O'Connor 2013).

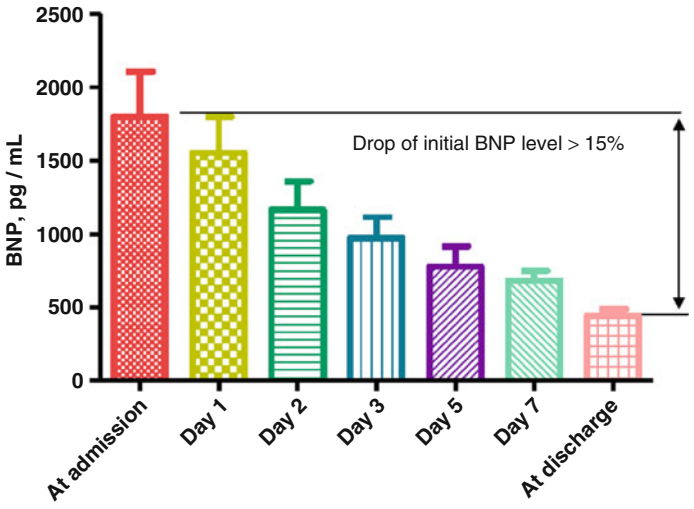

Fig. 2 Schematic trend of decreasing BNP plasma levels in patients with acutely decompensated heart failure. The plot shows a principal trend of decreasing BNP plasma levels with beneficial treatment strategy among inpatients with acutely decompensated heart failure. The data were pooled to obtain a mean and SEM (as *bars*) (The plot was constructed with data adapted from Bayes-Genis et al. (2004) and Kazanegra et al. (2001))

Serial Natriuretic Peptide Measurements as a Useful Predictive Tool in Chronic Heart Failure Management

The natriuretic peptides are important tools to establish diagnosis and prognosis for chronic heart failure patients. With the application of therapies for chronic heart failure, changes in both BNP and NT-pro-BNP parallel the benefits of chronic heart failure therapy that might be applied (Troughton et al. 2013). Among patients admitted with acutely decompensated chronic heart failure (ADCHF), patients who experienced complications were more likely to have much smaller changes (typically a 15 % decrease) in values of NT-pro-BNP compared to those who survived (about a 50 % decrease in NT-pro-BNP values from day 1 to day 7) (Bayes-Genis et al. 2004). Changes in the BNP level during early aggressive treatment have been closely associated with falling pulmonary wedge pressure in patients treated for decompensated CHF (Kazanegra et al. 2001). Overall, it has been asserted that serial measurements of natriuretic peptides could help to modulate more accurately the intensity of drug treatment in patients with chronic heart failure (Januzzi and Troughton 2013). Short-term therapeutic studies of inpatients have largely resulted in a statistically significant decline in BNP and NT-pro-BNP with clinical evidence of patient improvements (Wu 2006). However, serial BNP measurements may be useful in evaluating heart failure because there is a possibility to overcome the biological variability of natriuretic peptides by assessing such measurements (Fig. 2).

In contrast, many therapeutic studies involving long-term outpatient monitoring have produced changes in BNP/NT-pro-BNP that do not exceed the biologic variances (Wu 2013). Nevertheless, strategy of monitoring NT-pro-BNP and BNP to guide therapy cannot be universally advocated because there are still several open questions about the presumed role of natriuretic peptide-guided pharmacologic adjustment as a valuable strategy in this setting (De Vecchis et al. 2013a, b; Miller et al. 2005). Changes in serial BNP levels during the admission of the patients with acutely decompensated heart failure may be predictive of the clinical outcome; however, BNP has not been compared with other parameters, echocardiographic performances (even LVEF), and end points combined in-hospital deaths and post-discharge events (Cheng et al. 2001). In this study, patients had very high levels of BNP and no significant changes of circulating biomarkers during admission were found. Thus, the probability for a decrease of BNP/NT-pro-BNP plasma levels may be associated with the severity of heart failure and, probably, coexisting comorbidities. The so-called obesity paradox suggests that the presence of plasma BNP levels in patients with heart failure may be low when obesity is present (Adamopoulos et al. 2011). When the diagnostic utility of biomarkers for heart failure in older subjects in long-term care were examined, it was found that copeptin (ADM), MR-pro-ADM, and MR-pro-ANP, as well as common signs and symptoms, had little diagnostic value in comparison with BNP (Mason et al. 2013).

A trend of decreasing BNP/NT-pro-BNP plasma level may be a more important factor than the peak level of biomarkers (De Vecchis et al. 2013a, b). It was found that survivors had lower circulating levels of pre-discharged BNP than subjects who died (Ito et al. 2012). In fact, the biological variability of BNP/NT-pro-BNP plasma levels and close relation of circulating levels of biomarker with age, renal function, and comorbidities (such as obesity and diabetes) are the main limitations for the implementation of serial monitoring of BNP/NT-pro-BNP in routine clinical practice.

Continued BNP Home Monitoring in Heart Failure Patients

The hypothesis that adding a BNP level assay to a home monitoring regimen might add significant value in the early detection of heart failure decompensation in stable subjects after discharge was tested in the Heart Failure Assessment with BNP in the Home (HABIT) trial (Maisel et al. 2013). Using a finger-stick test (Alere HeartCheck System) that was specifically designed for the home monitoring of BNP levels in heart failure patients, an upward trend was found to correspond with an increased a risk of early readmission due to ADHF after discharge. Conversely, a downward BNP level trend indicated a risk decrease. Thus, the home monitoring of BNP in stable heart failure patients after discharge may provide sufficient information about the risk of early readmission within 30 days. The assessment of more durable continued monitoring efficacy is desirable to understand whether a novel option is beneficial.

Results of the Most Important Clinical Trials on BNP-Guided Therapy

The use of plasma levels of natriuretic peptides to guide the treatment of patients with chronic heart failure has been investigated in a number of randomized controlled and retrospective clinical trials; however, the results were controversial and the benefits have been high variable. It was found that BNP-guided therapy was not better than an expert's clinical assessment for beta-blocker titration in chronic heart failure patients (Beck-da-Silva et al. 2005). A retrospective study was dedicated to the assessment of serial BNP levels in patients receiving hemodynamically guided therapy for severe chronic heart failure (O'Neill et al. 2005). In patients with severe heart failure, BNP levels did not accurately predict serial hemodynamic changes, including left ventricular ejection fraction (LVEF) and left ventricle dimensions. In the Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study, patients treated with biomarker-guided care also had improved quality of life and significantly better reverse remodeling on echocardiography compared with patients who received standard care (Januzzi 2012). A multicenter randomized pilot trial (STARBRITE) tested whether outpatient diuretic management guided by BNP and clinical assessment resulted in longer survival and no hospitalization over 90 days compared with clinical assessment alone (Shah et al. 2011). There was no significant difference in the number of days alive and not hospitalized, change in serum creatinine, or change in systolic blood pressure. A BNP strategy was associated with a trend toward lower blood urea nitrogen; BNP strategy patients received significantly more angiotensin-converting enzyme inhibitors (ACEI), beta-blockers, and the combination of ACEI or angiotensin receptor blocker (ARB) plus beta-blockers (Shah et al. 2011). Not all investigators have confirmed that morbidity and mortality are improved in chronic heart failure patients receiving treatment guided by BNP levels, although significantly better clinical outcomes in BNP responders in comparison with non-responders were reported (Karlström et al. 2011).

The long-term prognostic impact of a therapeutic strategy using plasma brain natriuretic peptide levels was evaluated in the STARS-BNP Multicenter Study (Jourdain et al. 2007). A total of 220 New York Heart Association functional class II to III patients considered to be optimally treated with ACE inhibitors, beta-blockers, and diuretics by chronic heart failure specialists were randomized to medical treatment according to either current guidelines (clinical group) or a goal of decreasing BNP plasma levels <100 pg/ml (BNP group). The primary combined end point was chronic heart failure-related death or hospital stay for chronic heart failure. During the 15-month follow-up period, significantly fewer patients reached the combined end point in the BNP group (Jourdain et al. 2007). The results were mainly obtained through an increase in ACEI and beta-blocker adjusted dosages. Later, the TIME-CHF trial found that, in contrast to chronic heart failure with reduced LVEF, NT-pro-BNP-guided therapy may not be as beneficial in chronic heart failure patients with preserved LVEF (Maeder et al. 2013).

Although patients do not always improve after the implementation of BNP-guided strategy, the heterogeneous results of natriuretic-peptide guided therapy for chronic heart failure were confirmed by several meta-analyses (Li et al. 2013; Savarese et al. 2013). There was a significantly decreased risk of all-cause mortality and chronic heart failure readmission in the BNP-guided therapy group. Age and baseline BNP are the major determinants of chronic heart failure readmission when analyzed using meta-regression. In the subgroup analysis, chronic heart failure readmission significantly decreased in patients younger than 70 years or with higher baseline BNP ($\geq$2,114 pg/mL). When a separate assessment of variables was performed, it was found that NT-pro-BNP-guided therapy significantly reduced all-cause mortality and chronic heart failure-related hospitalization but not all-cause admission. However, BNP-guided therapy did not significantly reduce all-cause mortality, chronic heart failure-related admission, or all-cause admission. It was concluded that BNP-guided therapy did not significantly reduce mortality or morbidity. On the other hand, improved all-cause mortality and CHF-related admission rates were found in BNP-guided therapy cohorts.

Changes in follow-up circulating BNP levels versus peak BNP levels at admission or discharge may be able to stratify CHF patients at risk. The optimal population of these subjects might be an inpatient cohort with ADCHF at admission. Overall, data indicate a close association between BNP on the fifth day after admission due to ADCHF and cardiovascular risk. A marked decrease of circulating BNP may be a strong predictor of a decreased risk of death or new hospitalization, as well as other chronic heart failure-related clinical events. However, clinical trials have been shown that BNP-guided therapy in outpatients was associated with a similar risk of death and/or CHF-related hospitalization compared to a conventional clinical approach (De Vecchis et al. 2013a; Jourdain et al. 2007). Among outpatients with previous ADHF, a substantial improvement in cardiovascular event rates could not be demonstrated in patients treated with BNP-guided therapy compared with those undergoing the usual symptom-guided treatment. The question addressed to inpatients with ADHF is still unresolved and likely requires more investigation (De Vecchis et al. 2013b). On the other hand, some experts believe that novel biomarkers are needed for ADHF instead of natriuretic peptide, such as procalcitonin, ST2 protein, mid-regional ANP, galectin-3, copeptin, and probably fibroblast growth factor (Fig. 3). However, whether serial measurements of these marker levels improve prediction among patients with ADHF when compared with a traditional approach is still not understood.

Cost-Effectiveness of Natriuretic Peptide-Guided Therapy of CHF

Chronic heart failure management strategies have been shown to reduce re-hospitalizations and mortality, but the costs of treatment may cause concern in the current cost-conscious clinical setting. Overall, contemporary chronic heart failure management programs are under increasing pressure to demonstrate their cost-effectiveness in comparison with other approaches to improving patient

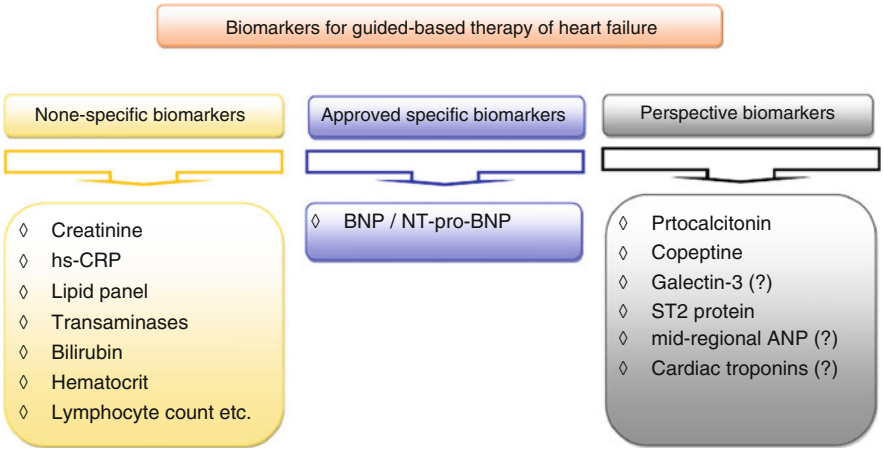

Fig. 3 Biomarkers for guided therapy of heart failure. *Abbreviations: hs-CRP* high sensitive C-reactive protein, *BNP* brain natriuretic peptide, *ANP* atrial natriuretic peptide

outcomes (Turner et al. 2008; Gonseth et al. 2004; Lambrinou et al. 2012). Risk predictive scores (e.g., The Seattle Heart Failure Model) that are based on combination of demographics, symptoms and signs of CHF, and several biomarkers (creatinine, lymphocyte count) significantly predict the survival of subjects with cardiac failure, as well as reduce medical resource use and costs (Levy et al. 2006). Online calculators allow physicians to unmask their knowledge around the risk and prognosis of the subjects observed (O'Connor et al. 2009). It is unclear whether the implementation of biological markers incorporated into risk scores has effective economic utility? It should be investigated if creating a biomarker risk predictive score is a more powerful tool to stratify the chronic heart failure subjects at risk when compared with contemporary predictive models.

Studies have shown that an introduction of BNP measurement in CHF management may be cost effective (Morimoto et al. 2004; Siebert et al. 2006). It was found that the optimal use of NT-pro-BNP guidance could reduce the use of echocardiography by up to 58 %, prevent 13 % of initial hospitalizations, and reduce hospital days by 12 % (Siebert et al. 2006). Moreover, NT-pro-BNP-guided assessment was associated with a 1.6 % relative reduction of serious adverse event risk and a 9.4 % reduction in costs, translating into savings of $474 per patient compared with standard clinical assessment. When a new disease management comparing usual care to home-based nurse care and a home-based nurse care group was investigated, it was concluded that NT-pro-BNP-guided chronic heart failure specialist care in addition to home-based nurse care was cost effective and cheaper than standard care, whereas home-based nurse care was cost neutral (Adlbrecht et al. 2011). Thus, BNP-guided chronic heart failure therapy may be considered as a highly effective strategy to minimize expenditures of the health care system for patients with chronic heart failure.

Limitations of the Natriuretic Peptide-Guided Therapy of CHF

Although the pooling of data derived from clinical trials demonstrates an overall effect of slightly significant improvement in clinical outcomes with a natriuretic peptide-guided approach, there are some relatively large studies that failed to document a significant clinical improvement in terms of mortality and morbidity using a natriuretic peptide-guided strategy (De Beradinis and Januzzi 2012). On the one hand, compared with standard management, biomarker-guided care appears to be cost effective, may improve patient quality of life, and may promote reverse ventricular remodeling. However, randomized clinical trials and real-world practice have affected the implementation of natriuretic peptide-guided therapy. On the other hand, the limitation of standard care strategies is evident from the suboptimal uptake and application of proven therapies documented in chronic heart failure registries (Komajda et al. 2005). Certain subgroups, such as the elderly and subjects at low to moderate cardiovascular risk, may respond in a less vigorous manner to the approach of a natriuretic peptide-guided strategy. In certain studies, patients treated with biomarker-guided care had superior outcomes when compared with standard heart failure management alone, particularly in younger populations, in patients with left ventricular systolic dysfunction, and when substantial reductions in natriuretic peptides were achieved in association with biomarker-guided care (McMurray et al. 2012). This may reflect the effects of age on chronic heart failure therapy. Therefore, subjects at different cardiovascular risk may have different responses to natriuretic peptide-guided therapy. Overall, a novel approach based on biomarker serial measurements requires serious adaptation in real clinical practice (Schou et al. 2013).

Novel Biomarker-Guided Approaches in the Management of CHF

Galectin-3 and ST2 protein, which reflect fibrosis and inflammation status, have been approved by the Food and Drug Administration as predictive biomarkers for heart failure patients (Carrasco-Sánchez and Páez-Rubio 2014). Unlike BNP/NT-pro-BNP, circulating galectin-3 and soluble ST2 protein concentrations are not affected by obesity, age, atrial fibrillation, or the etiology of heart failure (Piper et al. 2014; Lok et al. 2013). Therefore, both biomarkers have also shown significantly less individual variability over a 1-month time period compared with BNP (Piper et al. 2014; Lok et al. 2013). Although most of the studies involved patients with heart failure and systolic dysfunction, galectin-3 seems to have a more accurate role in heart failure patients with preserved LVEF then with reduced LVEF (Carrasco-Sánchez and Páez-Rubio 2014). Results of the ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study have demonstrated that the serial measurement of circulating galectin-3 adds incremental prognostic information to a conventional predictive score and closely ameliorates the prediction value of cardiac remodeling (Motiwala et al. 2013). Unfortunately, no clear effect of contemporary heart failure treatment on galectin-3 levels was found (Motiwala

et al. 2013). In the Val-HeFT study, baseline galectin-3 was not associated with a risk of all-cause mortality, but an increased biomarker level over time in heart failure patients was independently associated with worse outcomes (Anand et al. 2013). As in the PROTECT and Val-HeFT studies, no beneficial effect of serial measurement on outcomes was determined. The results of the Biomarkers in ACute Heart Failure (BACH) study suggested that the measurement of three biomarkers (MR-proANP, BNP, and NT-proBNP) allows for an increase in the predictive value for combination biomarkers, but the role of the approach in guided-based therapy remained unclear (Richards et al. 2013).

Serial measurements of midregion pro-ANP (MR-pro-ANP) and C-terminal provasopressin (copeptin) in ambulatory patients with heart failure were detected as possible approach for improving prognosis and clinical outcomes (Miller et al. 2012). It is well known that MR-pro-ANP and copeptin are precursor peptides of the natriuretic and vasopressin systems, respectively. As expected, a strategy based on the serial monitoring of MR-pro-ANP and copeptin combined with circulating cardiac troponin T (cTnT) might be advantageous in elucidating and managing outpatients with heart failure at high risk (Miller et al. 2012). The obtained results have shown that MR-pro-ANP, and to a lesser extent copeptin, seem to add support for an incremental value of serial measurements of BNP and cTnT over time (median = 18.9Insert Space instead off ±Insert Space instead off 7.8 months). Finally, this and other data indicate that two different phenotypes of heart failure may be detected using biomarkers: with and without beneficial response after intervention. It is reasonable to believe that biomarker-guided therapy might useful for initial and maintenance therapy of heart failure, as well as the inadequacy of an intervention requiring a dose-adjusted regimen or additional new drugs. However, numerous types of optimal components of biomarker panels for pre-treatment risk stratification and heart failure evolution remain a big question.

These findings have stimulated new attempts to investigate novel biomarkers, often with negative or equivocal results. Cardiac specific troponins were investigated in studies of patients with acute ischemic heart failure and ADHF. Both forms of troponins (cTnT and cTnI) have significantly predicted in-hospital mortality in patients after myocardial infarction, but serial measurements of their concentration did not confirm the ability of standard heart failure treatment to improve survival by reducing troponin levels (Xue et al. 2011; Peacock et al. 2008; Fonarow et al. 2008). However, a rapidly rising level of cTnI during admission was associated with worse outcomes when compared with limited or no increased levels. Overall, targeting a troponin level is possible but rarely achieved. Other novel biomarkers, such as fibroblast-growth factors and procalcitonin, may be indicators of reparation processes, but their use in guided therapy of heart failure is currently only in the proof-of-concept stage. Although procalcitonin seems to be an attractive option, evidence is only available for acute dyspnea, acute heart failure, and ADHF (Travaglino et al. 2014; Naffaa et al. 2014).

Novel biomarkers have shown great promise and stimulated much interest in their validation for acutely decompensated heart failure. However, there are no data about their superiority to conventional biomarkers, such as natriuretic peptides, in

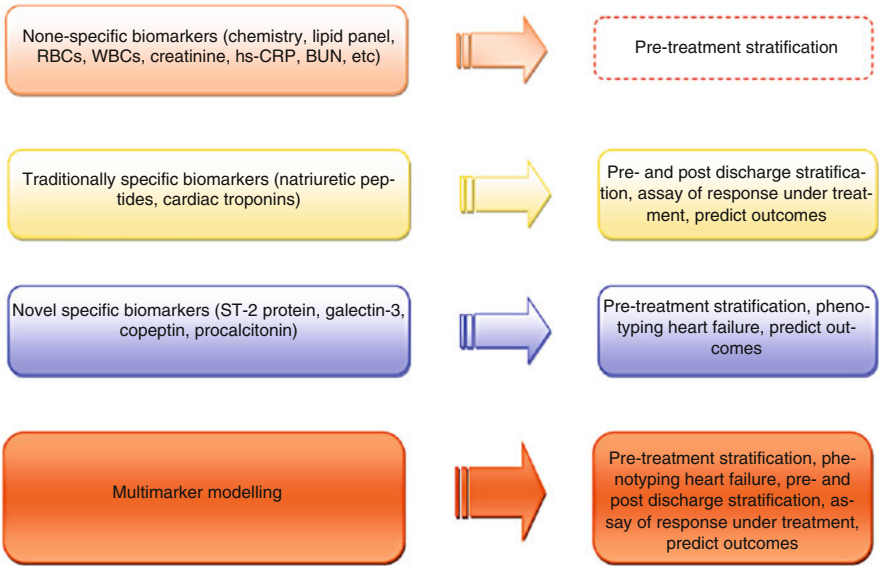

Fig. 4 Future possibilities for the implementation of biomarker-based strategies in heart failure treatment. *Abbreviations*: *RBCs* red blood cells, *WBCs* white blood cells, *hs-CRP* high sensitive C-reactive protein

postdischarge patients with chronic heart failure. In fact, biomarkers that indicate the phenotype of heart failure (ST-2 protein, galectin-3) are not suitable for serial monitoring in guided therapy. Conversely, natriuretic peptides are more optimal for serial monitoring. It has been postulated that future biomarker modelling will use a multimarker approach to stratify patients at risk and reassay therapy response (Fig. 4).

Potential Applications for Prognosis of Other Diseases or Conditions

BNP and NT-pro-BNP have good diagnostic and prognostic performance for heart failure. The serial measurement of circulating BNP/NT-pro-BNP may provide important and sufficient information about heart failure evolution under treatment. As expected, individualized treatment of heart failure based on biomarker monitoring may be more effective and safe then contemporary strategies. High biological variation of BNP/NT-pro-BNP concentration, as well as relation to renal function, aging, and comorbidities, should be considered as the main limiting factors for the implementation of serial measurements in routine clinical practice. Because there is a significant difference in the results of studies dedicated to biomarker-guided therapy of heart failure, serial measurements need to be interpreted carefully. Novel biomarkers (ST-2 protein, galectin-3, copeptin, procalcitonin) have shown great

promise and stimulated much interest in their validation for acutely decompensated heart failure; however, their superiority to conventional biomarkers, such as natriuretic peptides, in postdischarge patients with chronic heart failure is still not understood. A biomarker-based strategy may lead to an era of personalized medicine for chronic heart failure care in which therapy is optimized and costs are reduced.

Conclusion

Studies have suggested that a strategy of standard-of-care management together with a goal to suppress BNP or NT-pro-BNP concentrations leads to greater application of guideline-derived medical therapy and is well tolerated. In addition, a variety of novel (ST-2 protein, galectin-3, copeptin, procalcitonin) or already used (natriuretic peptides) biomarkers have been tested in small trials for heart failure management. Larger randomized clinical trials should be conducted in the future, with high statistical power to address the unresolved issues of natriuretic peptide-guided therapy in chronic heart failure. The future of heart failure management will probably involve an algorithm to use clinical assessment along with a biomarker-guided approach.

Summary Points

- This chapter focuses on serum-based biomarkers that are essential for guided management of patients with chronic heart failure.
- Biomarker-guided therapy of heart failure is an attractive aspect of this approach aimed at individualizing of the treatment strategy.
- Biomarker use for heart failure patients can help to determine the initial diagnosis, stratify patients at risk of acute or acutely decompensated heart failure, and monitor patients during the chronic phase to prevent readmission.
- Natriuretic peptide can guide therapy to prevent the onset of heart failure in at-risk primary care patients and likely assess hospital discharge readiness for patients with acutely decompensated heart failure.
- The concentrations of novel biomarkers, such as galectin-3 and soluble ST2 protein, are not affected by obesity, age, atrial fibrillation, or the etiology of heart failure. BNP/NT-pro-BNP may affect the probability of equivocal interpretation and controversial opinions.
- Phenotyping of heart failure biomarkers (ST-2 protein, galectin-3) is probably not suitable for serial monitoring in guided therapy.
- Circulating neurohumoral biomarkers (natriuretic peptides, copeptin, and procalcitonin) are more suitable and useful for biomarker-guided strategies in heart failure (Tables 1, 2, 3, 4, and 5).

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