Emerging Biomarkers in Heart Failure

Roland R.J. van Kimmenade and James L. Januzzi, Jr.*

BACKGROUND: Until recently, biomarker testing in heart failure (HF) syndromes has been viewed as an elective supplement to diagnostic evaluation of patients suspected to suffer from this condition. This approach to the use of biomarker testing contrasts with other cardiovascular diagnoses such as acute myocardial infarction, for which biomarkers are integral to disease process definition, risk stratification, and in some cases treatment decision making.

CONTENT: In this review we consider various perspectives on the evaluation of biomarkers in HF. In addition, we examine recent advances in the understanding of established biomarkers in HF (such as the natriuretic peptides), the elucidation of novel biomarkers potentially useful for the evaluation and management of patients with HF, and the growing understanding of important and relevant comorbidities in HF. We also review candidate biomarkers from a number of classes: (a) myocyte stretch, (b) myocyte necrosis, (c) systemic inflammation, (d) oxidative stress, (e) extracellular matrix turnover, (f) neurohormones, and (g) biomarkers of extracardiac processes, such as renal function.

SUMMARY: Novel applications of established biomarkers of HF as well as elucidation and validation of emerging assays for HF syndromes have collectively led to a growing interest in the more widespread use of such testing in patients affected by the diagnosis.

Go to your bosom; / Knock there, and ask your heart what it doth know

William Shakespeare, Measure for Measure

Heart failure (HF) has become a major burden in modern healthcare, not only in terms of morbidity and mortality for those directly involved, but also for society as a whole because of the expanding costs of caring for patients with HF. Although HF is increasingly encountered in medical practice, securing a correct diagnosis can be challenging, even for experienced clinicians. Furthermore, when the diagnosis of HF is made, it often remains difficult to assess stability of the patient. Lastly, ascertainment of whether optimal therapy for HF is being provided while avoiding the spectrum of side effects from standard medical or interventional therapy is a challenge.

It is in this context that interest in biomarkers of HF is on the rise, with an exponential increase in basic, clinical, and translational research focused on HF biomarkers (Fig. 1). Furthermore, the clinical introduction of testing for the natriuretic peptides, including B-type natriuretic peptide (BNP) and its amino-terminal propeptide equivalent, N-terminal proBNP (NT-proBNP), has fueled interest in the determination of biological standards for diagnosis, prognosis determination, and treatment of HF.

Through exploration of novel applications of established biomarkers and the study of more novel HF biomarkers (examples are summarized in Table 1), as well as elucidation of the intersection between HF and important comorbidities (such as renal dysfunction), we have developed a better mechanistic understanding of the biology of HF. In this review we discuss emerging concepts and questions in the field of HF biomarkers.

Background: What Makes a Biomarker in HF Useful?

When the merits of novel applications of already available biomarkers or the value of emerging tests are considered, the standards by which such biomarkers are judged should be kept in mind. Morrow and de Lemos introduced 3 criteria to evaluate the utility of a biomarker in cardiovascular medicine: such a biomarker should (a) be measurable at a reasonable cost on short notice; (b) add new information to the clinical workup; and (c) aid in the management of patients with a cardiogenic condition.
diovascular disease. The National Academy of Clinical Biochemistry has set forth comparable goals in a consensus document that states that a biomarker in HF ideally enables clinicians to (i) identify possible underlying (and potentially reversible) causes of HF; (ii) confirm the presence or absence of the HF syndrome; and (iii) estimate the severity of HF and risk of disease progression (3). Other investigators have further emphasized the importance of patient-based understanding of the biomarker result, and the behaviors that follow (4).

With the explosion of novel biomarkers available, it is reasonable to extend this important foundation. For a biomarker to be useful, the following conditions are necessary:

1. The method by which a novel biomarker is judged (including and especially compared to or in combination with other biomarkers) should be thorough: novel tests should be evaluated across a wide range of patients typical of the diagnosis for which the biomarker will be applied, and the statistical methods used to evaluate the biomarker (relative to clinical variables as well as other biomarkers) should be contemporary, rigorous, standardized, and fair.

2. Measurement of a novel HF biomarker (e.g., in blood, urine, or any easily obtainable tissue) should be easily achieved within a short period of time and provide acceptable accuracy, and assays for its measurement should have defined biological variation and low analytical imprecision.

3. The biomarker should primarily reflect important (patho)physiological processes involved in HF presence and progression; use of a biomarker that is reflective of heart disease but originates outside the myocardium is acceptable as long as such a biomarker provides independently useful information involved in the diagnosis, progression, or therapy of HF syndromes.

4. The biomarker must provide clinically useful information for caregivers (physician, nurses, and others) and patients to facilitate more swift and reliable establishment/rejection of a diagnosis and more accurate estimation of prognosis and to inform more successful therapeutic strategies. The information from such a biomarker should not recapitulate clinical information already available at the bedside, and must be additional to information provided by other biomarkers.

Besides the natriuretic peptides, none of the presently available or studied biomarkers meet these standards, although several may be close to doing so. Evaluating such markers is a complex process, however, because HF is not the result of one single patho-

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**Fig. 1. Number of HF biomarker reports in PubMed per year (left y axis) vs all publications (right y axis) during the last decade.**

A relatively remarkable increase in HF biomarker publication is noted after 2001, when BNP testing was introduced into clinical practice.
physiologic disease, but is a syndrome initiated by cardiac volume and/or pressure overload characterized by a broad range of pathophysiological features, presentation, and potential outcomes. Thus biomarkers in HF are most commonly classified according to the processes with which they are involved. Given the complementary and interactive nature of the biology of HF, biomarkers related to the diagnosis often combine well with markers from several pathophysiological categories (5, 6).

Table 1. Examples of candidate biomarkers in HF, divided into categories.

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>Neurohormones</th>
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<tr>
<td>CRP</td>
<td>Norepinephrine</td>
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<tr>
<td>TNF-α</td>
<td>Renin</td>
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<tr>
<td>TWEAK (TNF-like weak inducer of apoptosis)</td>
<td>Angiotensin II</td>
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<tr>
<td>IL-1, −6, −10, and −18</td>
<td>Aldosterone</td>
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<tr>
<td>LP-PLA2 (lipoprotein-associated phospholipase A2)</td>
<td>Arginine vasopressin, copeptin</td>
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<tr>
<td>Soluble TNF receptors 1 and 2</td>
<td>Endothelin-1</td>
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<tr>
<td>YKL-40</td>
<td>Urocortin</td>
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<tr>
<td>IL-1 receptor antagonist</td>
<td>Chromogranin A and B</td>
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<tr>
<td>Midkine</td>
<td>MR-proADM</td>
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<tr>
<td>Leucine-rich 2-glycoprotein</td>
<td>Myocyte injury and apoptosis</td>
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<tr>
<td>PTX3</td>
<td>Troponins I and T</td>
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<tr>
<td>CA-125</td>
<td>Myosin light-chain kinase I</td>
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<tr>
<td>S100A8/A9 complex</td>
<td>Heart-type fatty-acid-binding protein</td>
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<tr>
<td>Osteoprotegerin</td>
<td>Creatine kinase MB fraction</td>
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<tr>
<td>Serine protease PR3</td>
<td>sFAS (soluble apoptosis-stimulating fragment)</td>
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<tr>
<td>Soluble endoglin</td>
<td>Heat shock protein 60</td>
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<tr>
<td>Adiponectin</td>
<td>sTRAIL (soluble TNF-related apoptosis-inducing ligand)</td>
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<td><strong>Oxidative stress</strong></td>
<td><strong>Myocyte stress</strong></td>
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<td>Oxidized LDLs</td>
<td>BNP, NT-proBNP, MR-proANP</td>
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<td>MPO</td>
<td>sST2</td>
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<td>Urinary biopyrrins</td>
<td>GDF-15</td>
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<td>Urinary and plasma isoprostanes</td>
<td>Extracardiac involvement</td>
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<td>Urinary 8-hydroxy-2′-deoxyguanosine</td>
<td>RDW</td>
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<td>Plasma malondialdehyde</td>
<td>Cystatin-C, β trace protein</td>
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<td>Extracellular-matrix remodeling</td>
<td>NGAL, NAG [N-acetyl-β-(D)-glucosaminidase], KIM-1 (kidney injury molecule-1)</td>
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<tr>
<td>MMPs (MMP2, MMP3, MMP9)</td>
<td>β2-microglobulin</td>
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<td>TIMP1</td>
<td>Urinary albumin-to-creatinine ratio</td>
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<td>IL-6</td>
<td>Triiodothyronine</td>
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<td>Collagen propeptides</td>
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<td>N-terminal collagen type III peptide</td>
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<td>Myostatin</td>
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<td>Syndecan-4</td>
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<td>Galectin-3</td>
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Myocyte Stress/Stress

NATRIURETIC PEPTIDES

The role of the natriuretic peptides in HF is well established and has been extensively reviewed elsewhere (5–7). Nonetheless, important observations have been made recently about the biology of BNP and NT-proBNP, and clinical applications of a novel natriuretic peptide, midregional proatrial natriuretic peptide (MR-proANP) are emerging.
Important recent advances regarding the biology of BNP and NT-proBNP are worth mention. These 2 peptides derive from the same precursor molecule. The BNP gene natriuretic peptide B (NPPB) is rapidly upregulated by several stimuli, including cardiomyocyte stretch, injury, and hypoxia. In this context, a 134 amino acid prepropeptide is produced, with rapid cleavage and secretion of a 26 amino acid signal peptide. This process yields an important intermediate precursor, proBNP108, which is cleaved in various amounts by corin or furin to yield the 76 amino acid NT-proBNP and the 32 amino acid BNP (8) (Fig. 2). However, measurable amounts of proBNP108 also circulate (with some degree of peripheral cleavage as well). The uncleaved precursor cross-reacts with assays for both NT-proBNP and BNP, and analytical studies suggest that in HF patients proBNP108 provides diagnostic information comparable to BNP or NT-proBNP, whereas the ratio of BNP to proBNP108 may provide incremental prognostic information not provided by BNP alone (9).

BNP and NT-proBNP are generally accepted to be useful for the diagnostic evaluation of patients with acute dyspnea (10). Furthermore, natriuretic peptides are successful aids not only for diagnosing/excluding HF but also for predicting outcome in the diagnosis, in a manner as potent as—if not more powerful than—clinical factors. To this point, a recent metaanalysis analyzing data from 40 long-term prospective studies involving a total of 87,474 participants and 10,625 incident cardiovascular outcomes confirmed that a given proportional increment in BNP or NT-proBNP is similarly associated with increased cardiovascular risk (11). The prognostic value of BNP and NT-proBNP, together with the finding that therapy for HF modulates concentrations of these biomarkers, has led to their investigation as targets for HF therapy, with the concept that HF management “guided” by natriuretic peptides would be superior to standard HF therapy alone. Following a promising pilot study (12), subsequent heterogeneously designed studies have returned mixed results (13); despite this fact, recent metaanalyses suggest a significant mortality reduction related to natriuretic peptide–guided therapy. Thus this approach merits large-scale confirmation. Patients with HF due to systolic dysfunction appear to be more responsive to biomarker-guided care in which concentrations of the natriuretic peptide target must be low, and goal values must be achieved (or at least approached). In trials meeting these criteria, significant improvements in outcome were observed (14).
Although data supportive of natriuretic peptides are largely derived from trials of BNP or NT-proBNP, ANP was actually the first natriuretic peptide described, and just like related compounds from the B-type lineage, ANP increase is associated with HF. The major limiting factor for clinical application of ANP was that its measurement was challenging owing to analytical instability; recently a midregional MRpro-ANP assay (which leverages the biological stability of this peptide fragment) has been tested in a large prospective study (15). Concentrations of MR-proANP appeared to be as useful as those of BNP or NT-proBNP for diagnosis of HF, and the authors suggested that MR-proANP may be useful in situations in which BNP or NT-proBNP are less reliable, such as in patients who are obese or those with renal failure. Considerably more data are needed regarding MR-proANP before its widespread adoption occurs.

ST2

ST2 is a member of the interleukin (IL)-1 receptor family with a membrane-bound (ST2L) and a soluble form (sST2), and its production is stimulated by myocardial strain (16). The functional ligand for sST2 and ST2L is IL-33, which stimulates anti hypertrophic, antifibrotic, and antiapoptotic effects; the beneficial effects of IL-33 are mediated through ST2L, which results in resistance to apoptosis and reduction in fibrosis (17). In contrast, sST2 is thought to function as a decoy receptor, neutralizing the benefits of IL-33 (18).

Increases of sST2 may be observed in proportion to HF severity (19), but such increases are not universal, making sST2 less suitable as a diagnostic tool for HF. Importantly, however, increased sST2 values are biologically and clinically associated with ventricular remodeling (20) and are powerfully prognostic in a manner additive to natriuretic peptides and highly sensitive troponin. The importance of sST2 for prognosis has been demonstrated in patients suffering from acutely decompensated HF as well as chronic HF (19, 21); modulation of sST2 values by therapy also raises the potential role of this biomarker as a “guide” to HF therapy, as has been proposed for natriuretic peptides (22). The recent development of a highly sensitive and precise assay for sST2 measurement will now allow for examination of this assay in a broader range of patients (23).

GROWTH DIFFERENTIATION FACTOR 15

Recently, growth differentiation factor 15 (GDF-15) has gained interest as a biomarker in HF. GDF-15 is only weakly expressed in physiological circumstances, but its expression is significantly increased in response to inflammation and tissue injury. Increased expression of GDF-15 has been observed in the myocardium in HF and pressure overload in a manner reminiscent of BNP. GDF-15 is also expressed outside the myocardium, however, (24, 25). Indeed, GDF-15 expression is also upregulated in atherosclerosis (24, 26). Thus GDF-15 may be best viewed as a biomarker of cardiovascular, rather than purely cardiac, stress. Importantly, GDF-15 is also upregulated in certain cancers, as well as in pregnancy, and is found in a wide range of noncardiac tissue under states of injury. Although GDF-15 is not cardiac specific in its production, when cardiac GDF-15 overproduction occurs, the pathology of the heart associated with its increase seems clearer compared to other markers such as C-reactive protein (CRP). In a recent post hoc analysis from the Valsartan Heart Failure Trial, GDF-15 was independently associated with mortality in a model that included clinical prognostic variables, BNP, high-sensitivity CRP, and high-sensitivity troponin T. Increases in GDF-15 over 12 months were also independently associated with the risks of future mortality and first morbid event (27). Considerably more data regarding GDF-15 are needed, including analyses of more patients with acutely decompensated HF and chronic HF, as well as more specific data regarding possible therapeutic interventions for those with increased GDF-15 concentrations.

Myocyte Injury

Myocyte necrosis is prevalent in HF, and may result from tissue ischemia related to coronary artery disease as well as from “noncoronary” cell death in the failing heart, due to neurohumoral overstimulation, inflammation, or apoptosis. Increases in myocardial necrosis markers—particularly the troponins—in HF remain poorly understood, but are a common phenomenon. Furthermore, troponin concentrations may be dynamic in HF: many patients with low values for troponin subsequently develop increased values in follow-up in the absence of symptoms (28). Despite the poorly understood reasons for increased troponin in HF, the ramifications of such a phenomenon are considerable, with higher rates of cardiovascular events when troponin is increased in this context (29).

With the introduction of highly sensitive troponin assays, it is recognized that myocardial injury in HF is even more common than previously thought, but with similar prognostic ramifications. Lastini and colleagues first showed, using a highly sensitive troponin T method, that the vast majority of patients in an advanced chronic HF study had measurable to increased troponin values. In this study, the highly sensitive assay was superior to the conventional assay for prognosis, and was additive to BNP for this use (29). Similar studies supporting the prognostic value of highly sensitive troponin I or T assay measurements in chronic HF.
have followed (30, 31), as well as data showing the superiority of highly sensitive assays over conventional assays in acutely decompensated HF (21, 32). In most of these studies, the prognostic value of troponins was noted, even in the presence of other biomarkers such as natriuretic peptides, sST2, or copeptin.

Clinically, loss of cardiomyocytes, reflected in increases of troponin, is associated with a more decompensated clinical profile, and during follow-up, patients with increased troponin are more likely to have adverse ventricle remodeling (29). Troponins may be included in the list of biomarkers associated with ventricular remodeling/fibrosis. A therapeutic strategy for increased troponin values in HF syndromes remains to be elucidated; given the promise of the highly sensitive troponin assays in acutely decompensated HF (21, 32), the development of such a strategy should be viewed as a major priority.

**Inflammation**

Because inflammation is an important process in HF, mediators of inflammation have been studied intensively as potential biomarkers in HF. The first report of inflammatory markers in HF, which was published in 1956, said that CRP concentrations were increased in chronic HF patients and that absolute concentrations were indicative of severity of disease (33). CRP mediates several protective processes, but may also have deleterious effects in HF, such as upregulation of tumor necrosis factor α (TNF-α) and IL-6. Although recent studies confirmed a prognostic role for CRP in HF, it might be less suitable as a biomarker for HF because of its promiscuous role in various inflammatory processes and the lack of a therapeutic imperative associated with its increase. In addition, CRP may lose prognostic significance in models examining multiple biomarkers (34–36).

TNF-α contributes to the progression of HF through several mechanisms that modulate existing proteins (e.g., via stimulation of oxidative stress), and it also decreases the contractility of the heart via downregulation of sarcoplasmic reticulum proteins such as α myosin heavy chain (37, 38). TNF-α measurement predicts the development of HF in asymptomatic individuals as well as the progression in HF patients (especially men) (39, 40). Unfortunately, specific TNF-α blockade did not result in better outcome in HF patients (41). Use of TNF-α measurement to identify those most likely to benefit from such an approach has not been fully explored.

IL-6 directly affects cell-to-cell communications between cardiac myocytes and fibroblasts, and alterations in IL-6 concentrations are associated with cardiac dysfunction and alteration of the cardiac extracellular matrix. Because of these characteristics, IL-6 is sometimes discussed as a “remodeling” biomarker, much like sST2 or troponin. The predictive value of IL-6 for adverse outcome in HF may be independent of other inflammatory biomarkers, but IL-6 also lacks diagnostic specificity, and data are lacking in regard to whether individualizing care with IL-6 is possible (39, 40).

A promising inflammatory biomarker is pentraxin 3 (PTX3), which seems to play a cardioprotective role in HF (42). In a study with 196 HF patients, Suzuki et al. showed that increased PTX3 concentrations predicted outcome and that PTX3 was superior to CRP for this application (36). Matsubara and coworkers demonstrated that PTX3 concentrations were increased in HF patients with preserved ejection fraction and, by coronary sinus sampling, they showed that production takes place in the myocardium (34). Interestingly, administration of exogenous PTX3 rescued the phenotype of a PTX3 knockout mouse model with ischemic myocardial damage (43). Further investigation is needed, however, to determine whether PTX3 adds unique information to other promising biomarkers.

Although inflammatory markers may provide information that is prognostically compelling, they are generally nonspecific for heart disease. This characteristic, together with a lack of therapeutic ramifications associated with their use, makes this class of biomarkers less likely to be eligible for clinical application.

**Oxidative Stress**

Increased oxidative stress results from dominance of reactive oxygen species over endogenous antioxidant defense mechanisms, and through apoptosis and necrosis may directly decrease myocardial function. This decrease may occur via harmful effects on endothelial function, by activation of the renin–angiotensin–aldosterone system and the sympathetic nervous system, or via increases in inflammation. Many biomarkers discussed elsewhere are also involved in oxidative stress pathways. The most interesting biomarker of oxidative stress to discuss explicitly is myeloperoxidase (MPO).

MPO is an enzyme that is released by stimulated neutrophils and leukocytes and catalyzes the formation of reactive oxidants, free radicals, and nitric oxide–derived oxidants, which promote tissue damage. Reichlin et al. demonstrated that among patients with acutely decompensated HF, MPO concentrations >99 pmol/L identified patients with a higher 1-year mortality rate, even in the presence of BNP (44). Another study suggested that MPO predicts the development of HF over 7 years in individuals 65 to 75 years old, especially in those without a history of traditional risk factors of HF (45). Not all data for MPO are supportive for use in HF, however, and both the lack of therapeutic implications and the (pre)analyti-
cal issues associated with its measurement challenge its potential value (46).

**Extracellular Matrix Modeling**

The extracellular matrix of the heart is increasingly recognized to be important in the pathophysiology of HF progression; deleterious remodeling of the extracellular matrix is an important process that takes place through the degradation of collagen and other matrix proteins by collagenases, matrix metalloproteinases (MMPs), and mediated by tissue inhibitors of metalloproteinases (TIMPs). A recent report by Zile et al. suggests that parameters of extracellular matrix remodeling may be especially of interest for prediction of development of HF with preserved ejection fraction (47).

Measurement of degradation products of collagen provides a window into the activity of matrix breakdown: concentrations of both C-terminal propeptide and C-terminal telopeptide of type-1 collagen as well as the N-terminal peptide of procollagen type III identify the presence of fibrosis in HF syndromes (48) and may also identify those patients with HF who would benefit from specific treatments for HF, such as implantable cardioverter defibrillators (49, 50). Proteins involved in matrix breakdown—the MMPs and TIMPs—may be similarly useful for evaluation of HF patients. At least 25 MMPs have been described, and MMP2, MMP3, and MMP9 seem to play the largest role in the development of HF. Although increased MMP-3 and MMP-9 concentrations are associated with higher mortality rates in patients with HF due to left ventricular systolic dysfunction, MMP-9 predicted prognosis in these patients independently after adjustment for cofounders (51). In contrast, Frantz and coworkers found in 249 patients with chronic HF that TIMP1 (but not MMP9) predicted all-cause mortality, which may suggest that rather than absolute plasma concentrations, relative MMP vs TIMP activity may provide even better prognostic information (52).

Galectin-3 (Gal-3) is thought to represent a link between inflammation and fibrosis. Gal-3 is secreted by activated macrophages and is especially localized at sites of fibrosis and fibroblasts. Recombinant Gal-3 in vitro stimulates proliferation and collagen production of cardiac fibroblasts, and Gal-3 concentrations correlate highly with MMP2 and TIMP1 concentrations (53, 54). Gal-3 is increased in patients with HF, and although its diagnostic role in HF is of limited value relative to that of natriuretic peptides, Gal-3 is a reasonable predictor of intermediate and longer prognosis in HF and is additive to NP testing for this indication (55, 56). Comparative data between Gal-3 and other candidate biomarkers in HF are lacking, as are data regarding therapy interactions and the behavior of Gal-3 after therapy.

**Neurohormones**

Endothelin-1 (ET-1) is produced by the endothelium in response to angiotensin II, inflammatory mediators, and vascular shear stress, and is responsible for vasoconstriction, activation of reactive oxygen species, and ventricular remodeling (57, 58). The role of ET-1 in pulmonary hypertension is well established; however, Tang et al. more recently confirmed that ET-1 concentrations are associated with parameters of diastolic dysfunction and with prognosis in HF due to left ventricular systolic dysfunction (59). Whether increases of ET-1 identify specific benefits from agents that antagonize ET-1’s biological effects remains unclear, but this is a worthy area for exploration given the generally negative results in HF trials of these agents (60).

Urocortin-1 (UCN-1) is a vasoactive member of the corticotropin-released-factor family. In individuals with concentrations within reference intervals, UCN-1 provokes increases in heart rate, cardiac output, and coronary blood flow, and at very high concentrations it causes vasodilation and a decline in total peripheral resistance (61, 62). Although UCN-1 concentrations are typically higher in patients suffering from HF, results are heterogenous; (63, 64) the biomarker may be an independent predictor of prognosis in HF in the presence of other biomarkers, (59) but its final role in HF is clearly not elucidated and further studies are warranted. Nonetheless, given the links to vascular homeostasis in HF, UCN-1 remains of interest.

Arginine vasopressin (AVP) is an antidiuretic and vasoconstrictive hormone that is released from the hypothalamus in response to changes in plasma osmolality and hypovolemia; AVP production is upregulated in HF (65). AVP plays a role in the context of hypotension, a well-described, prognostically meaningful state in patients with HF (66). Unfortunately, AVP is difficult to measure owing to its short half-life and instability in vitro. A recently developed assay to detect the C-terminal portion of provasopressin (copeptin) has allowed the measurement of the very stable propeptide of this hormone (67). Copeptin predicts prognosis in HF, independently from troponin or NT-proBNP (31, 68), and is particularly of interest from a therapeutic perspective, because AVP receptor antagonists are available. Importantly, AVP receptor antagonists have not been routinely of benefit in patients with HF, a population of patients with derangement in sodium homeostasis from a wide variety of causes including excessive water retention (hypervolemic hypona-
tremia) as well as overexposure to diuretic agents (hypovolemic hyponatremia). Furthermore, in clinical practice, discernment of the correct cause of low sodium may be surprisingly difficult. In theory, copeptin might be able to discriminate the subset of hypervolemic hyponatremic patients who would benefit most from treatment with AVP receptor antagonists, (69) a hypothesis worthy of testing. Should copeptin be proven of use for this indication, it would represent a prime application of a biomarker to personalize HF care.

Adrenomedullin (ADM) causes vasodilatation via stimulation of nitric oxide production, and as a consequence is thought to be upregulated in HF as an endogenous compensatory mechanism for the hemodynamic abnormalities related to the diagnosis. Determination of circulating ADM is complex owing to its short half-life and the fact that it circulates in a bound form that is difficult to measure. Alternatively, measurement of midregional pro-ADM (MR-proADM) is now possible. MR-proADM is stable, and its measurement is not affected by protein binding. MR-proADM has been shown to be at least comparable to natriuretic peptides for predicting mortality in acutely destabilized HF (15, 70). Although the data regarding MR-proADM in HF are promising, considerably more information is needed, including the exact role MR-proADM would play relative to other novel markers, and what therapy interventions would be informed through its measurement.

**Extracardiac Involvement**

HF is not a phenomenon exclusively restricted to the myocardium, and may affect several (if not all) organ systems. Two syndromes related to HF (anemia and renal impairment) take on special importance in this context and are considered to be serious, prognostically important complications (71, 72).

Although anemia itself is important to presage outcomes in HF, specific hematologic measures may be even more prognostically meaningful. For example, red blood cell distribution width (RDW), a statistical parameter defined as the SD of erythrocyte size divided by the mean corpuscular volume, is of particular interest for measurement in HF. RDW is typically used as a tool for differentiating causes of anemia, but it may also be a powerful predictor of prognosis in chronic HF, even more powerful than classic hematologic parameters such as hemoglobin (73). Other investigators have confirmed the prognostic importance of RDW in both acutely decompensated and chronic HF (74, 75). More recently, it has been suggested that RDW may not be specifically a parameter of prognosis for HF or cardiovascular disease but may be an overall marker of wellness (76). The exact mechanism linking RDW with prognosis has not been fully elucidated; some data suggest that RDW reflects a combination of inflammation and impaired iron metabolism (77). The therapeutic response to an increased RDW remains unknown; given the wide availability of this biomarker and its low cost and ease of measurement, RDW should be given priority for investigation.

The interaction between renal impairment and HF has been discussed for more than a century (78). Although measures of renal function have long been used to monitor for the off-target side effects of HF therapies, recent focus has been given to biomarkers of renal function and markers of renal injury as being independently prognostically meaningful.

With respect to renal function markers, standard assays for creatinine and blood urea nitrogen are themselves independently prognostic in HF. In some studies, the results of calculated estimated glomerular filtration rate (eGFR) added considerably to prognostic models, and in function eGFR is dynamically interactive with natriuretic peptides (71). Indeed, in acutely decompensated HF, prognosis was particularly worse in patients with a falling eGFR and increased NT-proBNP, whereas the prognostic importance of changes in renal function were less clear in those with lower NT-proBNP concentrations. With more accurate measures of renal function may come more refined prognostic ability. Cystatin-C is a cysteine proteinase inhibitor that is produced by nearly all human cells and is released into the circulation. Clearance of cystatin-C depends entirely on glomerular filtration, making it a prototype marker of renal function (79). Cystatin-C is slightly superior to eGFR in detecting renal impairment, but shows a broad superiority for prognosis; importantly, increased cystatin-C concentrations are not only indicative of renal dysfunction, but also may be influenced by inflammation as well as the presence and severity of underlying heart disease (80). Cystatin-C concentrations strongly predict mortality and morbidity in acutely decompensated HF (81). In a similar fashion, β-trace protein—a novel measure of renal function—appears to be superior to eGFR for prognosis in HF. It is a low molecular weight protein synthesized in a broad range of tissues and may presage progression of chronic kidney disease. A recent study demonstrated that β-trace protein is additively prognostic to natriuretic peptides in patients with acutely decompensated HF (81). At present, although logic would dictate renal function markers could be used to specifically alter management of patients with HF (given their ability to identify changes in renal function related to congestion, declining cardiac output, or drug effects), the concept has not been specifically tested.
Renal injury markers may show similar promise for informing therapeutic decision making in patients with HF. Expression of neutrophil gelatinase-associated lipocalin (NGAL), a 25-kDa protein expressed in the proximal collecting tubule (82), is highly upregulated at an early stage of renal injury, and NGAL can be rapidly detected in the circulation or in urine (83, 84). NGAL was prognostic for mortality, hospitalization for HF, and worsening of renal function independent of eGFR in 90 very well phenotyped HF patients (85). In a similar fashion, kidney injury molecule-1 and N-acetyl-β-(D)-glucosaminidase are promising markers for the detection of renal injury in HF (86, 87). In theory, the use of a renal injury marker could supplement therapeutic decision making in the context of potentially nephrotoxic (and/or nephroprotective) therapies and/or strategies.

Summary

Above and beyond their present role for assisting in the diagnosis of HF, biomarkers will play an increasing role in the specific definition of the diagnosis, much as they presently do in the diagnosis, prognosis, triage, and management of patients suffering from acute myocardial infarction (88). Until recently, however, the evaluation and management of HF syndromes was considered a clinical exercise, with biomarkers playing a peripheral role. Emerging applications with established markers (such as “guiding” HF therapy with natriuretic peptides) are promising and will likely change the paradigm for standard HF care.

Several promising novel markers exist and bear testing and validation with the use of the strict criteria for evaluating their merit described in the Background section of this review. Although all of these markers have been shown to be potentially useful (Table 2), heterogeneous methods for their evaluation, unclear therapeutic implications associated with their increase, and the value added to natriuretic peptides limit the widespread application of novel tests. Ultimately, however, it is possible to envision the use of biologically “orthogonal” markers such as NT-proBNP (stress), sST2 (myocardial fibrosis/remodeling), highly sensitive troponin (myocardial injury), MR-proADM (hemodynamic stress), copeptin (salt/water derangement), and renal biomarkers to inform a wide palette of biological information regarding the past, present, and future clinical state of patients suffering from HF, a complex and high-risk diagnosis. Thus, individualized

### Table 2. Clinical relevance of promising novel biomarkers.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Diagnosis</th>
<th>Prognosis</th>
<th>Therapy guidance</th>
<th>Cardiac production</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP and BNP</td>
<td>++++</td>
<td>++++</td>
<td>+</td>
<td>Solely</td>
</tr>
<tr>
<td>MR-proANP</td>
<td>+++</td>
<td>++++</td>
<td></td>
<td>Likely similar to NT-proBNP/BNP</td>
</tr>
<tr>
<td>sST2</td>
<td>+</td>
<td>++++</td>
<td>?</td>
<td>Not exclusively</td>
</tr>
<tr>
<td>GDF-15</td>
<td></td>
<td>+</td>
<td>?</td>
<td>Not exclusively</td>
</tr>
<tr>
<td>Highly sensitive troponins</td>
<td>+</td>
<td>++++</td>
<td>?</td>
<td>Solely</td>
</tr>
<tr>
<td>CRP</td>
<td>–</td>
<td>++</td>
<td>?</td>
<td>No</td>
</tr>
<tr>
<td>TNF-α</td>
<td>–</td>
<td>++</td>
<td>?</td>
<td>No</td>
</tr>
<tr>
<td>IL-6</td>
<td>–</td>
<td>++</td>
<td>?</td>
<td>No</td>
</tr>
<tr>
<td>PTX3</td>
<td>–</td>
<td>++</td>
<td>?</td>
<td>Unknown</td>
</tr>
<tr>
<td>MPO</td>
<td>–</td>
<td>++</td>
<td>?</td>
<td>Not exclusively</td>
</tr>
<tr>
<td>Gal-3</td>
<td>–</td>
<td>+++</td>
<td>?</td>
<td>Not exclusively</td>
</tr>
<tr>
<td>ET-1</td>
<td>–</td>
<td>++</td>
<td>?</td>
<td>Not exclusively</td>
</tr>
<tr>
<td>UCN-1</td>
<td>–</td>
<td>++</td>
<td>?</td>
<td>Not exclusively</td>
</tr>
<tr>
<td>Copeptin</td>
<td>–</td>
<td>++</td>
<td>?</td>
<td>No</td>
</tr>
<tr>
<td>MR-proADM</td>
<td>–</td>
<td>++++</td>
<td>?</td>
<td>No</td>
</tr>
<tr>
<td>RDW</td>
<td>–</td>
<td>++++</td>
<td>?</td>
<td>No</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>–</td>
<td>++++</td>
<td>?</td>
<td>No</td>
</tr>
<tr>
<td>NGAL</td>
<td>–</td>
<td>++++</td>
<td>?</td>
<td>No</td>
</tr>
<tr>
<td>β-Trace protein</td>
<td>–</td>
<td>+++</td>
<td>?</td>
<td>No</td>
</tr>
</tbody>
</table>
therapeutic strategies developed from the use of such biomarkers may allow for a more personalized, biologically driven approach to HF care.

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References


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