AHA SCIENTIFIC STATEMENT

Role of Biomarkers for the Prevention, Assessment, and Management of Heart Failure

A Scientific Statement From the American Heart Association

BACKGROUND AND PURPOSE: Natriuretic peptides have led the way as a diagnostic and prognostic tool for the diagnosis and management of heart failure (HF). More recent evidence suggests that natriuretic peptides along with the next generation of biomarkers may provide added value to medical management, which could potentially lower risk of mortality and readmissions. The purpose of this scientific statement is to summarize the existing literature and to provide guidance for the utility of currently available biomarkers.

METHODS: The writing group used systematic literature reviews, published translational and clinical studies, clinical practice guidelines, and expert opinion/statements to summarize existing evidence and to identify areas of inadequacy requiring future research. The panel reviewed the most relevant adult medical literature excluding routine laboratory tests using MEDLINE, EMBASE, and Web of Science through December 2016. The document is organized and classified according to the American Heart Association to provide specific suggestions, considerations, or contemporary clinical practice recommendations.

RESULTS: A number of biomarkers associated with HF are well recognized, and measuring their concentrations in circulation can be a convenient and noninvasive approach to provide important information about disease severity and helps in the detection, diagnosis, prognosis, and management of HF. These include natriuretic peptides, soluble suppressor of tumorgenicity 2, highly sensitive troponin, galectin-3, midregional proadrenomedullin, cystatin-C, interleukin-6, procalcitonin, and others. There is a need to further evaluate existing and novel markers for guiding therapy and to summarize their data in a standardized format to improve communication among researchers and practitioners.

CONCLUSIONS: HF is a complex syndrome involving diverse pathways and pathological processes that can manifest in circulation as biomarkers. A number of such biomarkers are now clinically available, and monitoring their concentrations in blood not only can provide the clinician information about the diagnosis and severity of HF but also can improve prognostication and treatment strategies.

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Since the advent of natriuretic peptide testing for the evaluation of patients with suspected or proven heart failure (HF) in the year 2000, interest in biomarkers has grown exponentially.[1] Accordingly, a large number of preclinical and clinical analyses of biomarkers in HF have been completed, and the volume of publications in peer-reviewed literature focused on HF biomarkers has risen dramatically.[2] In addition, after the regulatory approval of the natriuretic peptides for clinical use, a number of newer biomarkers have received regulatory clearance for clinical testing in patients with HF,[3] and several others are currently in late-phase development. With such a rapid rise in the knowledge base of biomarker testing in HF, performance of a systematic assessment of the evidence in the space is justified, with consensus recommendations when appropriate.

The recommendations and suggestions/considerations listed in this document are, whenever possible, evidence based. An extensive literature review was conducted through December 2016, with references selected as appropriate. Searches were limited to studies, reviews, and other evidence conducted in human subjects and published in English. In addition, the committee reviewed documents related to the subject matter previously published by clinical practice guideline task forces from the American College of Cardiology Foundation and American Heart Association (AHA). References selected and published in this document are representative but not all-inclusive. To provide clinicians with a representative evidence base, whenever deemed appropriate or when published, it was felt that critical appraisal of the quality of study be maintained[4] and, whenever possible, robust statistical data be provided,[5] including interpretation of comparative studies between biomarkers.

ORGANIZATION OF THE WRITING COMMITTEE

The committee was composed of physicians and a pharmacist with a broad knowledge base in cardiac biomarker testing and deep expertise in the evaluation, care, and management of patients with HF. The authors' expertise included general cardiologists, HF specialists, clinical pharmacologists, and transplantation specialists, along with physicians with methodological expertise. The committee included representatives from the AHA Council on Clinical Cardiology; Council on Basic Cardiovascular Sciences; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Epidemiology and Prevention; Council on Functional Genomics and Translational Biology; and Council on Quality of Care and Outcomes Research.

DOCUMENT REVIEW AND APPROVAL

This document was reviewed by 2 official reviewers, each nominated by the AHA. All information on reviewers' relationships with industry was distributed to the writing committee and is published in this document.

This document was approved for publication by the governing bodies of the AHA.

RECOMMENDATIONS AND SUGGESTIONS/CONSIDERATIONS

To make certain that this document is aligned with the appropriate guideline statements but does not preempt those guidelines, the authors have opted to make reference to evidence-based clinical practice recommendations only and to refer the reader to the most recently published clinical practice guideline statement for more specific alignment with extant guidelines. Suggestions/considerations are included when the evidence does not warrant recommendations but there is still a desire to provide some guidance to the community.

SCOPE OF THIS SCIENTIFIC STATEMENT WITH REFERENCE TO OTHER RELEVANT GUIDELINES OR STATEMENTS

This scientific statement focuses on the use of biomarkers in HF. Some topics may have been reviewed in other clinical practice guidelines and scientific statements published by other working groups, including the American College of Cardiology/AHA task forces. The writing committee saw no need to reiterate the recommendations contained in those guidelines but chose instead to provide current recommendations and to clarify previous discrepancies. Some recommendations from earlier guidelines have been updated as warranted by new evidence or a better understanding of earlier evidence, whereas others that were no longer accurate or relevant or were overlapping were modified; recommendations from previous guidelines that were similar or redundant were eliminated or consolidated when possible.

DEFINITION OF A BIOMARKER

A 1998 National Institutes of Health working group on biomarkers definitions defined a biomarker as a biological marker that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacological responses to therapeutic interventions.[6] A definition proposed by the World Health Organization is any substance, structure, or process that can be measured in the body or its products and influences or predicts the incidence of outcome or disease.[6] Although biomarkers include physiological parameters,

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clinical images, and tissue specimen biopsies, this statement focuses on circulating biomarkers other than those that are routinely determined as part of clinical care such as electrolytes or hemoglobin.[7] Biomarkers can serve multiple roles. They can be used as a diagnostic tool for the identification of patients with an abnormal condition or as a tool for staging the extent of disease, as an indicator of disease prognosis, or for the prediction and monitoring of response to an intervention.[6] Morrow and de Lemos[8] set criteria a biomarker should fulfill to be clinically useful. Specifically, a useful biomarker should allow repeated and accurate measurements with a rapid turnaround time at reasonable cost, should provide information that is not already available from careful clinical assessment and its performance should be superior to other available tests, and should assist decision making and enhance clinical care. In an updated editorial, Maisel[9] suggested that a biomarker does not need to be both sensitive and specific, should have underlying pathophysiological relevance, and, if prognostic, should be used to either begin a certain treatment or monitor during that treatment.

PATHOPHYSIOLOGICAL ROLE OF BIOMARKERS IN HF

Biomarkers from blood can help detect the presence of HF, determine its severity, assess risk of future events, and guide therapy. The following discussion focuses on biomarkers that are not part of the routine clinical evaluation of patients but rather are obtained specifically to further assess prognoses and possibly direct HF therapy. Individual biomarkers are categorized according to their primary pathophysiological mechanism, although multiple pathways may also be involved.

Neurohormones

Systemic neurohormonal activation is a fundamental mechanism involved in the progression of HF. Activation of neurohormonal systems such as the renin-angiotensin-aldosterone system and sympathetic nervous system occurs in response to derangements in cardiovascular homeostasis. In particular, the stimulus for the production and release of these neurohormones appears to be related to arterial underfilling,[10] and it likely represents a primitive response to conditions that threaten the viability of the organism such as dehydration or blood loss. Although neurohormone-mediated vasoconstriction of arteries and veins and retention of salt and water by the kidney have short-term beneficial aspects, sustained activation (as occurs in HF) leads to increased load on the heart and ultimately drives maladaptive cardiac remodeling and progression of cardiac failure.

In general, plasma levels of neurohormones reflect severity of disease and, as a result, have been used as biomarkers in patients with HF. As initially noted with plasma norepinephrine,[11] worsening functional impairment is associated with higher levels of these neurohormones in the circulation.[12] Even patients with asymptomatic left ventricular (LV) dysfunction have elevated levels of neurohormones in their blood. When symptoms of HF appear, they rise according to severity. Although a strong association between neurohormone levels in the blood and the clinical course of patients with HF has been recognized for some time,[13] complex assays and handling procedures needed for processing neurohormones such as norepinephrine and epinephrine make clinical use impractical.

Markers of Extracellular Matrix Remodeling

Cardiac remodeling refers to a progressive series of changes in the size, shape, and function of the heart that are initiated by damage to the myocardium or increases in wall stress. Remodeling is a major factor in the development and progression of HF. It involves changes in both the cardiomyocytes and the makeup of the extracellular matrix (ECM). The latter consists of an intricate weave of (predominantly) collagen fibrils that play a vital role in maintaining the structural and functional integrity of the heart. ECM remodeling can be detected by measuring molecules of ECM composition or activity that are released into the circulation. These include collagen metabolites, factors that promote fibrosis, and matrix remodeling enzymes (Figure 1).

Measures of collagen fragments in the blood correlate with the intensity of remodeling and development of fibrosis in the heart as levels of amino- and carboxy-terminal propeptides increase as collagen is synthesized. Collagen degradation products such as carboxy terminal telopeptide of type I collagen released in the blood can also be used to assess remodeling.[14]

Although many enzymes are involved in regulating ECM deposition, a family of proteolytic enzymes that degrade fibrillar collagen, the matrix metalloproteinases (MMPs) and the tissue inhibitors of MMP, have been extensively studied in cardiovascular disease. Increased levels of MMPs or tissue inhibitors of MMP and the ratio between them have been associated with disease status. A role for profiling pathways of ECM degradation of these molecules has been postulated as a means of providing prognostic information.[15]

Inflammatory Mediators and Markers of Oxidative Stress

Tissue injury initiates an inflammatory response in which proinflammatory cytokines (and their receptors), cell adhesion molecules, and chemokines all participate as part of an innate stress response to help repair tissue injury (Figure 1). The response involves Toll-like receptors, which recognize endogenous host material released by cell injury or death, oxidized products, or damaged ECM

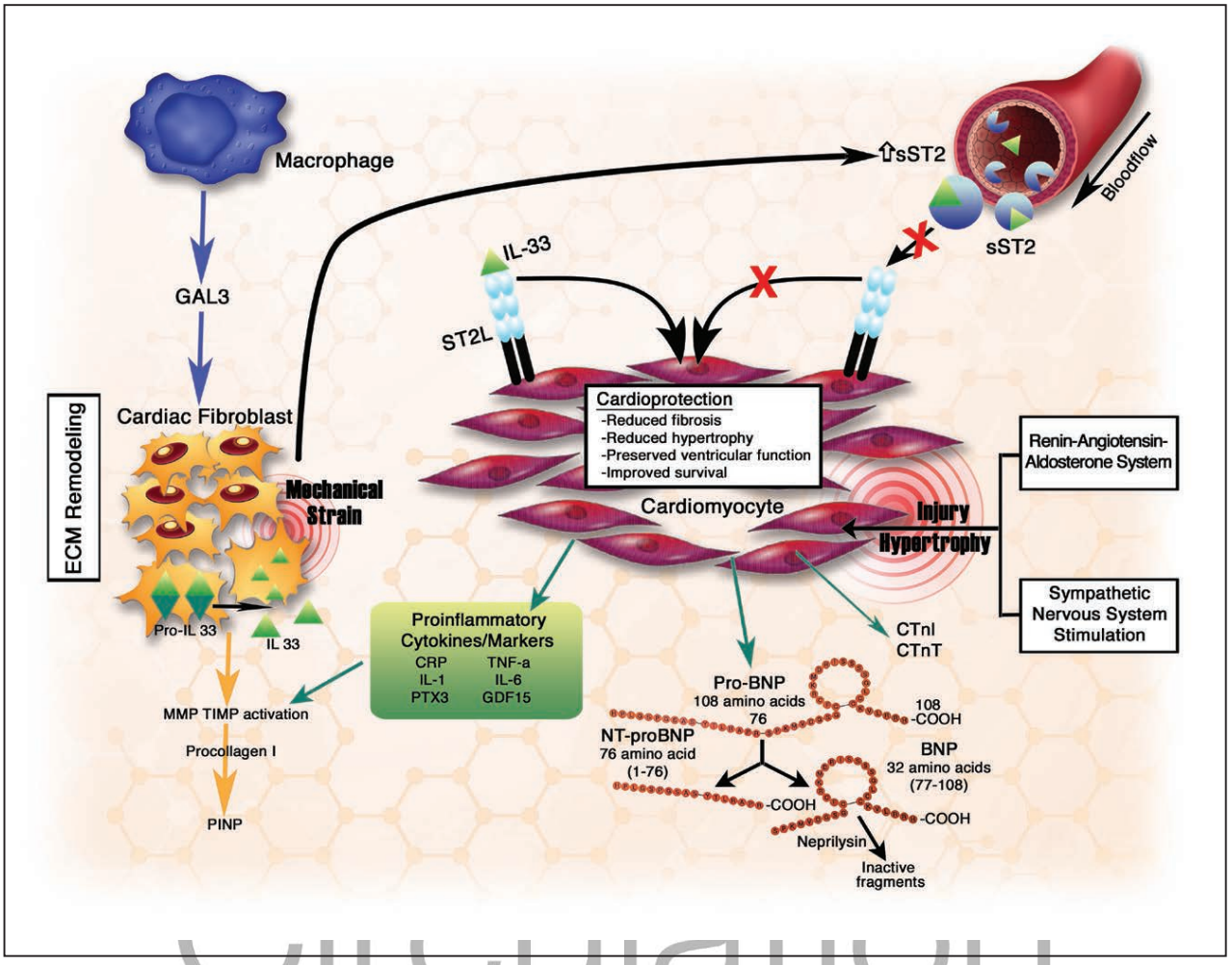

Figure 1. Mechanisms and responses to injury in heart failure.
BNP indicates B-type natriuretic peptide; CRP, C-reactive protein; cTn, cardiac troponin; ECM, extracellular matrix; GAL3, gelatinase-associated lipocain-3; GDF-15, growth differentiation factor 15; IL, interleukin; MMP, matrix metalloproteinase; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PINP, procollagen I intact N-terminal; PTX3, pentraxin 3; sST2, soluble suppressor of tumorgenicity 2; ST2L, ST2 membrane-bound receptor; TIMP, tissue inhibitor of matrix metalloproteinase; and TNF-a, tumor necrosis factor-α.

proteins.[16] Activation of these receptors leads to a proinflammatory response that, when sustained, adversely affects cardiac structure and function. The increased spillover into the circulation of these molecules makes them potentially useful as biomarkers that can be used to assess risk and to provide important insights into the mechanisms involved in the pathogenesis of HF.

Cytokines activate target cells by interacting with specific receptors that are anchored to the cell surface. The ectodermal portion of these receptors can be cleaved from the cell by proteolytic "sheddase" enzymes, releasing them into the interstitial space where they can diffuse into the circulation. The mediators that have proved most useful as biomarkers include the proinflammatory cytokines tumor necrosis factor-α, IL (interleukin)-1, and IL-6 (Figure 1). GDF-15 (growth differentiation factor 15), a member of the transforming growth factor-β cytokine superfamily, is a marker of cell injury and inflammation. CRP (C-reactive protein), a member of the pentraxin family, is produced predominantly in the liver as part of the systemic response to inflammation and has been used to assess patients with HF.[17]

ST2 (suppressor of tumorgenicity 2) exists in both membrane-bound and soluble forms and is a member of the IL-1 receptor family, which binds to IL-33, a mediator of inflammatory disease. IL-33/ST2 signaling is responsible for the maladaptive processes of myocyte hypertrophy and enhanced extracellular protein deposition in fibrosis. Binding of IL-33 to membrane ST2 produced by increased myocardial biomechanical force elicits an antihypertrophic and antifibrotic response. This cardioprotective effect is negated by the soluble form of ST2 (sST2), which acts as a decoy to prevent binding of IL-33 to membrane-bound ST2 (Figure 1). This leads to myocardial death and tissue fibrosis, reduced cardiac function, and acceleration of disease progression when concentrations of sST2 are elevated.[18]

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Gal-3 (galectin-3), a β-galactoside–binding lectin member of the galectin family,[19] is also a marker of inflammatory response in HF. Expression of Gal-3 is increased in activated macrophages and through interaction with proteins and molecules in the heart. This appears to stimulate pathological remodeling, particularly by inducing fibroblast proliferation and collagen deposition[20–23] (Figure 1).

Myocyte Injury and Myocyte Stress

In patients with HF, myocardial oxygen delivery may be compromised by low cardiac output or reduced diastolic blood pressure that results in a reduction in coronary perfusion. Elevations in ventricular filling pressures worsen the situation by reducing the driving gradient that moves blood through the coronary circulation. The oxygen supply is often decreased when demand is increased by elevations in ventricular wall stress and neurohormone-mediated augmentation of heart rate and contractility. This "perfect storm" created by the imbalance between supply and demand results in myocardial ischemia, particularly in vulnerable subendocardial regions. Inflammation, oxidative stress, and neurohormonal activation have been postulated to play a role in causing cardiomyocyte injury,[24] and cardiomyocyte apoptosis or development of hibernating myocardium may also be involved.[25]

Release of the myofibrillar proteins such as TnT (troponin T) and TnI (troponin I) occurs in patients with HF in the absence of an acute coronary event. Although many patients with HF have underlying coronary artery disease, a measurable rise or fall of troponin can occur in such patients, even in the absence of significant epicardial coronary artery stenosis, indicating that other factors are involved. Although the underlying mechanisms have not been clearly delineated and may vary between patients, subendocardial ischemia, created by supply:demand mismatch, likely plays a major role.[26]

BNP (B-type natriuretic peptide) and its amino-terminal cleavage equivalent (NT-proBNP) are released into the circulation directly from myocardium as a result of end-diastolic wall stress as a result of increases in volume or pressure.[27–29] Unlike ANP (atrial natriuretic peptide), which is stored in granules in the atria, BNP appears to be synthesized in bursts. The initial product of the *BNP* gene, pre-proBNP$_{1\text{-}134}$ undergoes rapid removal of 26 amino acids to form proBNP$_{108}$. This peptide is then cleaved by the proteolytic enzymes furin and corin, resulting in the formation of NT-proBNP$_{1\text{-}76}$ and BNP$_{1\text{-}32}$, with only the latter molecule being biologically active.[30–32] Clearance of BNP$_{1\text{-}32}$ is carried out by the natriuretic peptide receptor-C and neutral endopeptidases in the circulation and by passive excretion through the kidneys and other organs with high blood flow, whereas NT-proBNP appears to be cleared largely by organs with high blood flow such as muscle, liver, and kidney[33–35] (Figure 1). Although the kidneys appear able to clear both natriuretic peptides equally well, the half-life of NT-proBNP is longer than that of BNP (120 versus 20 minutes).[36,37]

Other Biomarkers

MicroRNAs are short, noncoding RNA sequences that regulate gene expression at the posttranscriptional level by targeting the 3′-untranslated region of mRNA sequences. They are stable in the circulation and have been explored as potential biomarkers in coronary artery disease, myocardial infarction, hypertension, diabetes mellitus, viral myocarditis, and HF.[38]

ASSESSING RISK FOR INCIDENT HF

Predicting Incident HF Risk in the Community

The lifetime risk for HF is substantial. It is strongly age dependent, with incidence rates of <1% below the age of 50 and up to 30% at advanced age (>80 years).[39] Because HF is a heterogeneous and multifactorial disease, the prediction of the risk for new-onset HF is difficult. However, in the past decade, several studies have addressed this issue, and several clinical parameters have emerged that, alone or in a model, may be of help to predict new-onset HF. These studies are, however, generally limited by sample size, by the inability to distinguish between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), and by the absence of (one or several) biomarkers in the prediction models.

Natriuretic Peptides

Natriuretic peptides have demonstrated value for predicting new-onset HFrEF in a number of large, high-quality, prospective cohort studies. In the FHS (Framingham Heart Study), BNP and urinary albumin-to-creatinine ratio emerged as key biomarkers in predicting new-onset HF.[40] These biomarkers significantly improved the model C statistic and enhanced risk reclassification on top of a base model comprising age, sex, body mass index, systolic blood pressure, hypertension treatment, diabetes mellitus, current smoking, ratio of total to high-density lipoprotein cholesterol, valvular heart disease, and prevalent myocardial infarction (Framingham Heart Score). Other data further support the potential utility of natriuretic peptides to predict the long-term development of HF. Older adults with initially low biomarker concentrations that demonstrated a rise in both NT-proBNP >25% and cardiac troponin T (cTnT) >50% over time were found to be at greater risk for systolic dysfunction, HF events, and cardiovascular death.[41]

Another potential strategy explored a multimarker approach for predicting new-onset HF. In the PREVEND

study (Prevention of Vascular and Renal End Stage Disease), a total of 13 biomarkers were evaluated for their value in the prediction of new-onset HF on top of a clinical base model.[42,43] Again, the overall additive value of biomarkers was small. Multivariably adjusted, NT-proBNP, midregional proANP, high-sensitivity (hs) TnT, cystatin-C, and urinary albumin excretion were predictive for new-onset HF. In a subset of patients with high baseline risk determined by clinical parameters, the best model for prediction of new-onset HF included NT-proBNP, TnT, and urinary albumin excretion. Several other studies demonstrated similar findings.[41,44–48]

With respect to superiority of one of the natriuretic peptides, aggregate evidence supports the best predictive value of BNP and NT-proBNP, stronger than ANP and NT-proANP.[49] Furthermore, in the CHS (Cardiovascular Health Study), it was shown that physical activity decreased the likelihood for an increase in NT-proBNP and hs-troponin over time, and this was associated with a lower risk of new-onset HF.[50]

Troponins

In both apparently healthy individuals in the general population (stage A HF) and asymptomatic individuals with stable cardiovascular disease (stage B HF), detectable levels of cTn have been demonstrated. With modern and widely used assays, the prevalence of detectable troponin in stage A and B HF is in the 1% to 5% range,[51,52] whereas with hs-assays, most studies have found that as many as 50% to 80% of asymptomatic individuals have levels above the limit of detection,[53,54] with some levels at or above the 99th percentile.[55,56] Higher troponin levels are associated with established HF risk factors, including diabetes mellitus, LV hypertrophy, chronic kidney disease, and elevated natriuretic peptide levels, but not prior myocardial infarction or coronary calcium.[51–53] Interestingly, elevated troponin concentrations generally have a stronger relation with future risk of HF than ischemic events.[54] Serial measurements may improve risk classification.[53]

Markers of Renal Dysfunction

Renal dysfunction, expressed by creatinine or cystatin-C, has been reported to be a strong predictor of new-onset HF. Gottdiener et al[57] and Lam and colleagues[58] reported that higher serum creatinine was associated with increased HF risk. In the FHS,[40] among routine laboratory biomarkers, urinary albumin-to-creatinine ratio emerged as an independent predictor for HF, whereas in the PREVEND study, urinary albumin excretion alongside NT-proBNP and TnT was identified. In summary, renal markers have consistently emerged as predictors of new-onset HF; however, further comparative studies are necessary to identify which renal biomarkers are best predictors of new-onset HF in the population.

Emerging Markers of Inflammation: Gal-3, sST2, and GDF-15

Wang et al[48] explored the value of Gal-3 for predicting new-onset HF in the FHS and found that in a fully adjusted model that included BNP and Gal-3, a modest independent predictive value was found for new-onset HF (hazard ratio [HR], 1.23 per 1-SD increase; P=0.02). In PREVEND, Gal-3 did not predict incident HF in the entire cohort. However, in a subset with high-risk subjects, Gal-3 added marginally to the base model for predicting new-onset HF.[42]

Among 3428 subjects in the FHS,[48] elevated concentrations of sST2, hs-TnI, GDF-15, and BNP were independently associated with incident HF during a mean follow-up of 11 years. Recent data from a population-based Finnish study[48] with a follow-up of 15 years showed that baseline sST2 levels did not predict incident HF.[59] Collectively, these markers have additive prognostic value in risk models for new-onset HF. Furthermore, the addition of a multimarker score to clinical variables could potentially lead to an improvement in discrimination and reclassification.[48]

Other Biomarkers

Other biomarkers have been associated with new-onset HF. Higher levels of ceruloplasmin have been linked to new-onset HF in the ARIC study (Atherosclerosis Risk in Communities).[60] Furthermore, inflammatory markers have been evaluated for predicting new-onset HF. In the ABC study (Health, Aging, and Body Composition), IL-6, tumor necrosis factor-α, and CRP were associated with new-onset HF, but when all 3 markers were added to the model, IL-6 emerged as the strongest marker.[17]

Suggestions/Considerations for Clinical Practice/Public Health Initiatives

1. In community-based populations, measurement of natriuretic peptides (BNP or NT-proBNP) or markers of myocardial injury (TnI or TnT) alone adds prognostic information to standard risk factors for predicting new-onset HF.[40,48,53,61–63]
2. Measurement of several new biomarkers, including sST2, Gal-3, GDF-15, and markers of renal function, alone or in a multimarker strategy, may be useful for providing additional risk stratification.[40,42,48,64]

BIOMARKERS FOR THE DIAGNOSIS OF HF

Biomarkers in conjunction with the clinical and physical assessment can provide greater diagnostic accuracy than the physical assessment alone. The natriuretic peptides are the best-established and best-evaluated markers to help in the proper diagnosis and exclusion of HF.

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Numerous studies have addressed this issue, and 2 large meta-analyses have summarized the available data.[65,66] These data convincingly demonstrate that natriuretic peptide levels improve diagnostic performance in several settings, including in patients with asymptomatic LV dysfunction,[67,68] in patients presenting with dyspnea and fatigue,[69–72] and in those presenting to the emergency department (ED) with acute dyspnea.[73–85]

The Role of Natriuretic Peptides in the Diagnosis of Decompensated Acute HF

Decompensated acute HF (AHF), regardless of the EF, often (if not always) is accompanied by cardiomyocyte injury. This injury may be reversible (no cell necrosis) or irreversible (with cell necrosis). Repetitive hospitalizations for HF are associated with increased morbidity and mortality, in part as a result of cardiomyocyte injury.

Natriuretic peptides are most commonly used to support the diagnosis of HF in patients with dyspnea.[86] In the Breathing Not Properly study, BNP accurately diagnosed HF in patients presenting to the ED with dyspnea, with a sensitivity of 90% and specificity of 76% at a cutoff of 100 pg/mL.[75] NT-proBNP was found to have even higher sensitivity for excluding HF at a cutoff of 300 pg/mL.[87] The sensitivity and specificity of NT-proBNP were identical to those of BNP if an NT-proBNP threshold of 900 pg/L was used, but to improve positive predictive value, age-related cutoffs of 450 pg/mL for <50 years, 900 pg/mL for 50 to 75 years, and 1800 pg/mL for >75 years[88] are recommended.

The diagnostic strength of natriuretic peptides is their high sensitivity for ruling out HF; however, as the value increases, HF becomes more likely. Defining "rule-in" cutoffs for HF is complicated because multiple factors influence natriuretic peptide levels (detailed below). Proposed rule-in cutoffs are the age-related values presented above for NT-proBNP and a value >400 pg/mL for BNP.[88]

Clearly, natriuretic peptides serve a key role in managing HF; as with any biomarker, there are caveats to their interpretation (Table 1).[89–91] Although natriuretic peptide values may be elevated in non-HF disease states, this does not reflect a false positive but a pathological process causing ventricular stress, which requires a different interpretation of natriuretic peptides. This is analogous to "slight" elevations of hs-troponins, which do not reflect plaque rupture but rather myocyte injury and necrosis.

Interpreting natriuretic peptides in the setting of other confounders may be challenging. Underlying factors such as age and sex influence BNP, but their overall impact is less significant compared with comorbidities such as cardiac, pulmonary, and renal disease, which are likely to increase natriuretic peptides above current thresholds for HF. Therefore, cautious interpretation of concentrations is important, especially in the presence of ≥1 confounders. Elevations of BNP and NT-proBNP in the setting of pulmonary hypertension and pulmonary embolism are related to right ventricular dysfunction and have significant prognostic value independently of underlying LV dysfunction. Similarly, higher natriuretic peptide levels associated with mitral regurgitation are directly correlated with mortality and onset of HF and should be carefully considered. The accuracy of natriuretic peptides for the detection of HF is reduced in the setting of atrial fibrillation and sepsis, and careful interpretation is warranted.[86] Concentrations of BNP or NT-proBNP can also be lower than expected in the setting of presumed AHF. The chief caveat in this respect is the decrease seen with increasing body mass index.[90] In flash pulmonary edema, natriuretic peptides may be slightly elevated at presentation but can rise markedly over time despite adequate treatment. In many cases, adequate diuresis is required before natriuretic peptide concentrations are evaluated because euvolemic natriuretic peptide levels may be more accurate to predict prognosis and guide therapy.

Table 1. Confounders Influencing the Interpretation of Natriuretic Peptides

Higher Natriuretic Peptide Levels Than Expected	Lower Natriuretic Peptide Levels Than Expected
Increasing age*	Obesity
Acute coronary syndrome*	Flash pulmonary edema
Renal insufficiency	Pericarditis/tamponade
RV dysfunction*	Genetic polymorphisms
Atrial fibrillation	End-stage cardiomyopathy
Pulmonary hypertension*	
Pulmonary embolism*	
Anemia/high-output states*	
Sepsis	
Mitral regurgitation*	

RV indicates right ventricular.
*Delineates likely elevation from ventricular stretch.

Contemporary Clinical Practice Recommendation[39,92]

Measurement of BNP and NT-proBNP is useful to support clinical judgement for the diagnosis of ambulatory and acute decompensated patients, especially in the setting of clinical uncertainty.[93]

Biomarkers for the Potential Diagnosis of HFpEF

The current diagnosis of HFpEF is one of exclusion that is based on the clinical presentation of HF but with EF values being normal or near-normal range on the basis of imaging evaluation. There is a need for appropriate

biomarkers that can properly diagnose HFpEF and provide pathophysiologically relevant classification. This is an area of active research.

Natriuretic Peptides

Circulating levels of natriuretic peptides are elevated in patients with HFpEF compared with subjects without HF but are lower than concentrations seen in patients with HFrEF. In patients with HFpEF, increased BNP or NT-proBNP is directly related to increased LV end-diastolic wall stress.[29] In addition, levels of BNP and NT-proBNP fall when LV diastolic pressure decreases in response to volume reduction. Patients with HFpEF have a small LV cavity and thick LV walls with end-diastolic wall stress being much lower than in HFrEF, even in the setting of high diastolic pressures, thus producing a lower stimulus for BNP production.

Partition values for diagnostic criteria of BNP ≥100 pg/mL and NT-proBNP ≥800 pg/mL have been suggested to support the diagnosis of HFpEF.[92] However, factors independent of LV diastolic pressure and diastolic stress may affect BNP levels in patients with HFpEF. As in patients with HFrEF, for any given LV diastolic pressure in patients with HFpEF, BNP levels are lower in obese patients and higher in women, older patients, and patients with concomitant pulmonary disease (chronic obstructive disease, pulmonary hypertension, pulmonary embolus), renal dysfunction, and atrial fibrillation. Patients with these significant comorbid states may have elevated BNP levels even in the absence of HFpEF. Therefore, partition values may need to be adjusted in patients with HFpEF and these comorbid states. For example, some obese patients with HFpEF have a BNP of 60 to 100 pg/mL when in symptomatic HF; BNP levels rise in these patients after weight loss from bariatric surgery to levels >100 pg/mL.[94–96]

Markers of Diastolic Dysfunction

A significant proportion of patients with HFpEF have diastolic dysfunction.[97] Cardiac stress releases marker candidates such as insulin growth factor–binding protein-7, which is released by the myocardium in the setting of abnormal filling pressure. Insulin growth factor–binding protein-7 has been correlated with echocardiographic parameters of diastolic dysfunction in both HFrEF and HFpEF.[98,99] Insulin growth factor–binding protein-7 levels correlate with indicators of diastolic dysfunction such as increased E/E', E/A ratios, left atrial volume index, and right ventricular systolic pressure. This may provide a means to identify patients with HFpEF and diastolic dysfunction in the future after further confirmation.

Collagen Homeostasis and Matrix Markers

Myocardial fibrillar collagen is composed primarily of collagen I and III; changes in both are important. Fibrillar collagen content results from the balance in the following processes: procollagen synthesis, postsynthetic procollagen processing, and posttranslational collagen cross-linking and collagen degradation. Biomarkers that reflect each of these steps in collagen homeostasis have been characterized; however, collagen synthesis and degradation and determinants of degradation have thus far been the best studied in HFpEF.

MicroRNAs

In addition to protein and peptide biomarkers, a number of plasma microRNAs were examined in patients with HFpEF. MicroRNAs are products of noncoding genes that act to repress protein translation and can result in increased or decreased collagen content. Changes in microRNA 29a, 1, 21, and 133a were associated with myocardial fibrosis in patients with HFpEF. MicroRNAs have not yet been applied as diagnostic or prognostic biomarkers in patients with HFpEF.

Multibiomarker Panels

Although each individual biomarker can be considered a single entity, data suggest that the predictive accuracy is significantly increased when these biomarkers are used together in a multibiomarker panel. For example, a multibiomarker panel (selected from 17 biomarkers, including natriuretic peptides) of MMP-2, MMP-8, tissue inhibitor of MMP-4, and procollagen-III N-terminal peptide provided a prediction algorithm for HFpEF with both good sensitivity and acceptable specificity (area under the curve=0.79).[100] Taken together, this multibiomarker panel in patients with HFpEF suggested that the presence of a shift in collagen homeostasis to a profibrotic condition provides good diagnostic discrimination and carries a poor prognosis.

Novel Biomarker Candidates in HFpEF

Novel biomarkers candidates are urgently needed for HFpEF to improve its diagnosis and to better understand its pathophysiology. Specific markers that help to categorize the patient population to permit targeted evaluation of novel therapies will represent a major step forward for this condition with currently limited options (Table 2).

BIOMARKERS AND PROGNOSIS IN HF

Chronic HF

In addition to the routinely obtained clinical laboratory values of hemoglobin, electrolytes, and renal and liver function, there is an increasing interest in the utility of other biomarkers that are implicated in pathogenesis of HF, reflecting hemodynamic, inflammatory, injury, and

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Table 2. Summary of Applications of Biomarkers to HFpEF

Biomarker	Application to HFpEF	Reference
Markers of hemodynamic load		
Natriuretic peptides		
BNP, NT-proBNP	Correlate with LVED wall stress	29
	Support diagnosis	39, 92
	Predict mortality, HF events	101, 102
	Guide therapy	39, 103
Markers of diastolic dysfunction		
Insulin growth factor–binding protein 7	Correlates with diastolic dysfunction	98
	Predicts mortality and functional capacity	99
Markers of inflammation		
↑sST2	Correlates with elevated LVEDP	104
	Supports diagnosis	105
	Predicts mortality, HF events	48, 106, 107
↑Gal-3	Supports diagnosis	108
	Predicts mortality, HF events	109–113
Markers of matrix turnover		
Collagen propeptides		
↑PICP, PINP, PIIINP	Support diagnosis	100, 114–117
	Predict mortality	118
Collagen telopeptides		
↑CITP	Supports diagnosis	114, 116, 119
	Predicts HF events	117
MMPs		
↑MMP-1	Supports diagnosis	115
↑MMP-2	Supports diagnosis	100, 114, 116
↑MMP-8	Supports diagnosis	100
↑MMP-9	Supports diagnosis	114, 116
TIMPs		
↑TIMP-1	Supports diagnosis	115
↑TIMP-4	Supports diagnosis	115, 120
↑Osteopontin	Predicts mortality, HF events	118

BNP indicates B-type natriuretic peptide; CITP, carboxy-terminal telopeptide of collagen type I; Gal-3, galectin-3; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LVED, left ventricular end-diastolic; LVEDP, left ventricular end-diastolic pressure; MMP, matrix metalloproteinase; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PICP, procollagen I C-terminal propeptide; PINP, procollagen I intact N-terminal, serum; PIIINP, type III procollagen peptide; sST2, soluble form of suppressor of tumorgenicity 2; and TIMP, tissue inhibitor of matrix metalloproteinase.

neurohormonal changes and remodeling or stress profile of the myocardium, cardiac myocyte, ECM, or cardiovascular system. These biomarkers have been identified as powerful adjuncts to standardized clinical care in determining the prognosis of chronic HF.

Natriuretic Peptides: BNP or NT-proBNP

Natriuretic peptides, specifically BNP and NT-proBNP, are useful for supporting clinical judgement for the diagnosis or exclusion of HF, especially in the setting of chronic ambulatory HF.[121]

Measurement of BNP or NT-proBNP is useful for establishing prognosis in chronic HF. Elevated BNP or NT-proBNP levels parallel HF disease severity, assessment by New York Heart Association (NYHA) class, elevated filling pressures, or worse hemodynamics[121–124] and are suggestive of worse clinical outcomes and mortality in chronic HF.[125–128] Further data demonstrated that each 100-pg/mL increase in BNP was associated with a 35% increase (95% confidence interval [CI], 22–49; *P*=0.096) in the relative risk of death.[129]

Biomarkers of Myocardial Injury: cTnT or Cardiac Troponin I

Modest elevations of circulating cTn levels are found in patients with HF without ischemia or coronary artery disease, suggesting ongoing myocyte injury or necrosis in affected patients.[130–134] Elaboration of cTn is associated with impaired hemodynamics,[130] progressive LV dysfunction,[131] and increased mortality rates[130,134] in patients with chronic HF. Decrease in levels over time with treatment is associated with a better prognosis than persistent elevation in patients with chronic HF[131] or AHF.[135]

With a highly sensitive new assay, cTn levels are detectable in the majority of the patients with HF,[136,137] a finding that predicts adverse outcomes, including mortality,[136,137] and retains additional prognostic value at previously undetectable concentrations. In the Val-HeFT trial (Valsartan Heart Failure Trial) of 4053 stable patients with chronic HF without overt evidence of myocardial ischemia or infarction, detectable TnT levels were associated with an increased risk of death (HR, 2.08; 95% CI, 1.72–2.52) and first hospitalization for HF (HR, 1.55; 95% CI, 1.25–1.93) at 2 years.[137]

Soluble ST2

Compared with other biomarkers such as natriuretic peptides, advantages of sST2 include that its concentration is not affected by age, renal function, or body mass index. sST2 levels correlate with prognosis in HF. In an analysis of >1100 patients with chronic HF,[138] patients with the highest decile of sST2 concentration had an HR of 3.2 (*P*<0.0001). A level of 35 pg/mL in the outpatient setting appears to clearly delineate low-risk patients from those with high risk. In a post hoc analysis of 1650 patients with HFrEF in the Val-HeFT trial, sST2

levels were mostly in the normal range.[126] Nevertheless, sST2 was associated with features of worse HF and was nonlinearly associated with increased risk of adverse outcomes. However, in a multivariable model that included clinical variables and NT-proBNP, baseline sST2 did not improve the ability to discriminate patients who did or did not have a poor outcome, although it did increase the sensitivity of 1-year outcome predictions. Additionally, an increase in sST2 from baseline to 12 months was associated with an increased subsequent risk of poor outcomes, suggesting that repeat measurement of sST2 may be useful for monitoring patients.[139] In a similar fashion, Gaggin and colleagues[140] examined concentrations of sST2 in carefully managed patients with chronic HFrEF. In this analysis, sST2 concentrations were superior to NT-proBNP, hs-TnT, and GDF-15 for predicting cardiovascular events. As with the Val-HeFT results, serial measurement added considerably to a baseline value for sST2; those patients demonstrating a rise from <35 ng/mL to above this cutoff had an adjusted HR of 3.64 (P<0.001) for adverse outcome. In this same cohort, sST2 concentrations were found to interact with β-adrenergic blocker therapy.[141]

Galectin-3

In patients with chronic ambulatory HF, elevated levels of Gal-3 may be modestly associated with mortality[110,142] among both patients with HFrEF[143] and those with HFpEF,[110] although the association with outcome in chronic ambulatory HF is less strong than for other biomarkers.

Midregional Proadrenomedullin

In the BACH study (Biomarkers in Acute Heart Failure),[144] MR-proADM (midregional proadrenomedullin) was associated with mortality at 3 months with a prognostic value beyond natriuretic peptides. In the Australia-New Zealand Heart Failure Study, above-median levels of MR-proADM predicted increased risk of mortality (risk ratio, 3.92; 95% CI, 1.76–8.7) and of HF hospitalization (risk ratio, 2.4; 95% CI, 1.3–4.5) independently of traditional clinical and echocardiographic factors.[145] Treatment with carvedilol reduced the risk of death or HF hospitalization in patients with above-median levels of NT-proBNP, MR-proADM, or both. Although promising for predicting short-term prognosis, more studies are needed to determine the utility and prognostic value of MR-proADM in HF.

Other Emerging Biomarkers

There is a large body of literature examining the role of other biomarkers such as proinflammatory cytokines and chemokines, biomarkers of remodeling or ventricular hypertrophy, biomarkers of oxidative stress, neurohormones, and biomarkers of renal injury that may be involved in the pathogenesis, progression, decompensation, or complications in chronic HF (Table 1). Table 1 provides a summary of such biomarkers that have been implicated in HF.

It is possible that multimarker strategies that combine biomarkers may ultimately prove beneficial in guiding HF therapy in the future. It should be kept in mind that to be useful for a large, general population, a screening test or biomarker should be sensitive, accurate, reliable, easily standardized, and inexpensive. The assay should be relatively easy to perform and analyze. Most emerging biomarkers currently do not fulfill these criteria.

Acute HF

Episodes of acutely decompensated HF are associated with decreased survival, high rates of rehospitalization, and high costs of care.[146,147] In an analysis of the OPTIMIZE-HF registry (Organized Program to Initiate Life Saving Treatment in Hospitalized Patients With Heart Failure), the risk of death within 90 days of hospitalization was 8.6%.[148] Furthermore, approximately a third of patients are rehospitalized within 90 days of discharge,[149] and the 1-year survival rate of ≈70% after HF hospitalization has not improved significantly over time.[150]

A challenge in the management of AHF syndromes is the accurate identification of patients at highest risk of these adverse events, death, and rehospitalization. The majority of patients with signs and symptoms of AHF undergo initial evaluation and treatment in the ED. Clinicians lack the ability to accurately assess prognosis, and patients who at are lower risk may end up hospitalized and those who are at higher risk may be discharged to home.[151] Circulating biomarkers have emerged as central not only to the diagnosis but also to the risk stratification of patients with AHF.

In addition to routine clinical laboratory tests and physiological findings, a number of biomarkers have gained acceptance for their utility to assist in HF prognostication. Several serum biomarkers are independently associated with outcomes during the initial HF hospitalization and the postdischarge period. Cardiac biomarkers reflect the pathophysiological aspects of AHF and include natriuretic peptides (myocyte stretch), cTns (myocyte necrosis), CRP (inflammation), copeptin (neurohormonal upregulation, vasoconstriction, and water retention), MR-proADM (vascular stress), and sST2 and galactin-3 (myocardial remodeling and fibrosis).[152]

Outcomes may be improved by treatment intensification among high-risk patients, and risk assessment is important to ensure that interventions such as aggressive pharmacological or device-based therapy are appropriately implemented. As an example, patients estimated to be at the highest risk might benefit from more intensive monitoring in a critical care unit setting rather than a general medicine floor. Similarly, at time of dis-

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charge, risk assessment can identify patients who may derive the greatest benefit from palliative care services, referral for consideration of advanced HF therapies, or enrollment in disease management programs.[153] Thus, biomarker-guided prognostication may aid resource allocation.

Biomarker-assisted prognostication also facilitates patient-provider communication and the shared decision-making process.[154] Clear communication about prognosis helps to establish patient-caregiver expectations about the short- and long-term goals of care. Finally, biomarker-guided risk prediction can aid patient selection for clinical trials by identifying patients at highest risk of clinical events.

Natriuretic Peptides

Values of BNP and NT-proBNP have modest correlation,[36,155] and either can be used in patient care settings, with the understanding that their absolute values and cut points are not interchangeable.[39] Concentrations of BNP and NT-proBNP measured at either the time of admission or discharge can help to distinguish a patient's level of risk for subsequent events.

Initial BNP level on presentation with dyspnea to an acute care setting is a powerful predictor of short- and long-term outcomes.[145,155–159] Among the >48 000 patients with a recorded BNP level enrolled in ADHERE (Acute Decompensated Heart Failure National Registry), there was a nearly linear relationship between admission BNP quartiles and in-hospital mortality.[160] Compared with 1.9% for patients in the lowest quartile, the rate of in-hospital mortality was 6% for those in the highest quartile (odds ratio, 2.23; 95% CI, 1.91–2.62; $P<0.0001$). This relationship was independent of other standard markers of risk in this population. Furthermore, these findings were true for patients with HF with either preserved or reduced systolic function.[158] In a study of 325 patients presenting to the ED with dyspnea, those with baseline BNP levels >480 pg/mL had a cumulative 6-month probability of an HF event of 51%[159] compared with 2.5% in those with a BNP <230 pg/mL. Elevated BNP at presentation is also associated with increased morbidity, and patients in ADHERE with a BNP ≥840 ng/mL were more likely to require mechanical ventilation, admission to the intensive care unit, and longer lengths of stay.[88]

Likewise, baseline NT-proBNP is also strongly predictive of outcomes.[160,161] In a post hoc analysis of the PRIDE Study (ProBNP Investigation of Dyspnea in the Emergency Department), after multivariate adjustment, Januzzi et al[160] identified initial NT-proBNP concentration >986 pg/mL as the strongest predictor of 1-year mortality (HR, 2.88; 95% CI, 1.64–5.06; $P\leq0.001$).

Both BNP and NT-proBNP levels improve with treatment during HF hospitalization.[146, 156,162–164] Studies have found predischarge BNP to be a stronger marker of postdischarge outcomes than either baseline or percent change in BNP during hospitalization.[146,156,163,165] Linking data from OPTIMIZE-HF with Medicare claims, Kociol et al[146] found that a Cox proportional hazards model including discharge BNP performed best and that discharge BNP was the single most important characteristic for predicting 1-year mortality or death/HF hospitalization. In a separate cohort, predischarge BNP ≤430 pg/mL has similarly been demonstrated to have strong negative predictive value for 30-day readmission (96%; 95% CI, 80–100).[156]

Predischarge NT-proBNP is also more strongly associated with outcomes than admission levels.[162,164] In 182 consecutive patients admitted with HF, the risk of death or readmission was higher for those who did not have a significant reduction in NT-proBNP, defined as a decrease >30%, compared with those who did (HR, 2.03; 95% CI, 1.14–3.64).[162] The risk was even higher for those who had a 30% increase compared with those who had a 30% decrease (HR, 5.69; 95% CI, 3.23–11.01).

Cardiac Troponins

Troponin levels add incremental prognostic information to that obtained from other clinical markers and physical examination findings and should be included in the initial evaluation of AHF as part of early risk assessment. Elevations in cardiac troponin I (cTnI) and cTnT both correlate with poor prognosis and are associated with impaired hemodynamics, progressive decline in LV systolic function, and reduced survival.[130,166–173] Among patients enrolled in ADHERE, a positive troponin was defined as either cTnI >1.0 μg/L or cTnT >0.1 μg/L.[174] Of HF episodes, 6.2% were associated with a positive troponin, and in-hospital mortality for troponin-positive patients was 8.0% compared with 2.7% for those who were troponin negative (odds ratio, 2.55; 95% CI, 2.24–2.89; $P<0.001$).[174] A separate analysis of 2025 patients hospitalized with HF found that cTnI levels >0.5 μg/mL were independently associated with short-term mortality (adjusted HR, 1.49; 95% CI, 1.25–1.77; $P<0.001$).[175] There was a dose-dependent response between troponin level elevation and subsequent outcomes. Troponin elevation during AHF is also associated with increased morbidity, and patients with detectable levels have required longer lengths of stay and increased resource use such as intensive care unit level of care.[174] Likewise, a negative troponin level can help to identify a lower-risk patient.[174] In an analysis of 538 patients presenting to an ED with HF, negative troponin and systolic blood pressure >160 mm Hg were the only 2 independent markers of inability to discharge within 24 hours or adverse cardiac event within 30 days.[176]

In regard to serial measurement, troponin elevation at any time over the course of hospitalization confers substantial increased risk of mortality.[135,177] In a small study

of 62 patients, persistently elevated cTnT levels >0.02 ng/mL were predictive of higher rates of death and hospitalization for HF.[172] One-year mortality was 71% for patients whose troponin remained elevated compared with 45% for those whose level decreased (P<0.05).

Beyond natriuretic peptides and troponins, multiple other biomarkers are associated with prognosis among patients presenting with AHF. sST2 levels correlate with NYHA classification, left ventricular ejection fraction, creatinine clearance, BNP, NT-proBNP, and CRP.[107,178] However, unlike the natriuretic peptides, sST2 is not related to age, prior diagnosis of HF, body mass index, ischemic type of HF, or atrial fibrillation.[107,179] The relative independence of sST2 from prevalent comorbidities represents a potential advantage of sST2 for prognostication over the commonly used natriuretic peptides.[107]

Patients with AHF who have elevated concentrations of sST2 are at increased risk of death.[106,107,178–181] sST2 concentrations can predict mortality as early as a few months from presentation and out through at least 1 year. In a study of 593 patients admitted to the ED with dyspnea, Januzzi et al[180] found that although sST2 was not as useful as NT-proBNP for predicting a diagnosis of HF, concentrations of sST2 were higher in patients with HF compared with those with dyspnea resulting from other causes (p < 0.01) and that an elevated sST2 concentration was independently associated with increased 1-year mortality. In a separate study, sST2 was associated in a separate cohort with a 2-fold increase in 1-year mortality.[107] Similar to chronic HF, serial measurement adds value to a baseline concentration of sST2. Several cohorts have now shown that posttreatment concentrations of sST2 more powerfully predict death compared with baseline values[182–184] and in general provide superior prognostic information to other markers, including BNP or NT-proBNP, in this regard.[155]

In addition to the natriuretic peptides, there is a substantial literature on other biomarkers at the time of AHF hospitalization and subsequent risk. cTns have been shown in some studies,[175,177,185,186] but not others,[187] to predict postdischarge events. Some of these variations may be the result of differences in patient characteristics, troponin assay characteristics (which vary markedly[188]), or possible publication bias. Biomarkers thought to reflect cardiac remodeling (sST2 and Gal-3) have also been evaluated as tools to predict early postdischarge events. Both baseline sST2 values at the time of hospitalization and changes in sST2 during short-term therapy have been associated with postdischarge outcomes.[107,180,182,183,189,190] High levels of Gal-3 at discharge also predict later events[111,112] and have been shown to independently predict early HF rehospitalization in a pooled analysis.[191] This could potentially be useful for selecting high-risk patients not previously identified with traditional risk factors. CRP and other inflammatory markers,[192,193] endothelin,[194] MR-proADM,[195] and copeptin[196,197] have also been shown to be independently associated with clinical outcome after AHF in some data sets. In general, studies analyzing the additive value of multiple markers typically find newer markers to be modestly complementary to standard risk factors and natriuretic peptide levels.[155,190]

Biomarker Panels

Studies have demonstrated that use of combined biomarkers can improve risk stratification.[88,130,145,155,167,198] An analysis of ADHERE found that a multimarker strategy for assessment of patients hospitalized with HF added synergistic information.[88] The interaction between BNP and troponin was not significant, and the combination these 2 biomarkers had additive prognostic value. In >42 000 AHF hospitalizations, admission BNP and troponin were predictive of in-hospital mortality.[88] Detectable troponin was defined as cTnI ≥1.0 ng/mL or a cTnT ≥0.1 ng/mL.[199] Mortality risk varied ≈5-fold on the basis of initial BNP and troponin levels.

Similarly, the prognostic value of sST2 has been shown to be additive to that of NT-proBNP such that patients with elevations in both biomarkers experienced the highest 1-year mortality and subjects with low values for both had the lowest.[180] The association between sST2 and NT-proBNP remained intact out to 4 years from presentation. However, natriuretic peptides may not always predict mortality, particularly in the setting of a low sST2 level, and thus sST2 may enable reclassification of risk.[107] The combination of Gal-3 and NT-proBNP for identifying those at highest risk also appears to be superior to evaluation of either biomarker alone.[112] Accordingly, strategies of combining biomarkers have proven useful for improving risk stratification.[106] However, to guide clinical practice in the acute care setting as it relates to the evaluation of biomarkers for the purpose of risk assessment, further research is necessary to define which biomarker panels optimize prognostication of short- and long-term outcomes.

HF With Preserved EF

Large, retrospective, community-based studies have reported that outcomes are similar for patients with HFpEF and HFrEF.[200,201] However, a more recent meta-analysis using individual patient data in >40 000 patients found that although mortality and morbidity rates in patients with HFpEF were high, mortality was approximately a third lower in patients with HFpEF compared with those with HFrEF. Nevertheless, it is important to be able to predict outcomes in these patients, and several biomarkers have tested this association in patients with HFpEF and have been found to be useful to predict prognosis in HFpEF.

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Natriuretic Peptides

Several studies have shown that natriuretic peptides are independently associated with mortality and morbidity in patients with HFrEF, but relatively fewer studies have tested their prognostic value in patients with HFpEF.[202,203] A post hoc analysis of the I-Preserve study (Irbesartan in Heart Failure With Preserved Ejection Fraction) in 3480 well-characterized patients with HFpEF was the largest study to show that levels of NT-proBNP are elevated in HFpEF but to a lesser extent than in HFrEF. However, the prognostic information provided by NT-proBNP appears to be similar in the 2 types of HF. In a multivariable Cox regression model, NT-proBNP above the median of 339 pg/mL was independently associated with a nearly 80% increase in the risk of the primary end point of all-cause mortality and prespecified cardiovascular hospitalizations, >100% increase in all-cause mortality, and 77% increase in hospitalization for worsening HF.[204] Moreover, as observed in HFrEF, changes in NT-proBNP over time were also associated with outcomes: A rise in NT-proBNP was associated with an increase in risk of cardiovascular death or HF hospitalization, and a fall was associated with a trend toward a decrease in risk, suggesting that NT-proBNP may be a useful marker to monitor prognosis in this condition.[102]

Markers of Inflammation and Immune Signaling

Biomarkers such as Gal-3 and sST2 may reflect the degree of immune activation and subsequent cardiac remodeling, including fibrosis.[23,48,105,109,110,205,206] A number of studies have demonstrated that Gal-3 is increased in HFpEF and predicts worse outcomes in this population, but concentrations tend to be lower than in HFrEF.[110] In patients with HFpEF, Gal-3 >17.8 ng/mL indicates low risk; Gal-3 of 17.9 to 25.9 ng/mL, intermediate risk; and Gal-3 >25.9 ng/mL, higher risk.[110,142,207] Whether these values should be adjusted for comorbidities in HFpEF has not been established.

sST2 is increased in HFpEF and is associated with diastolic dysfunction, increased myocardial stiffness, fibrosis, and decompensation.[208] In patients with HFpEF, sST2 partition values >32 ng/mL predict poor prognosis. Whether these should be adjusted for comorbidities in HFpEF has not been established.

Contemporary Clinical Practice Recommendations[39]

1. Measurement of BNP or NT-proBNP and cTn at the time of presentation is useful for establishing prognosis or disease severity in patients with acutely decompensated HF.
2. Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis is reasonable for additive risk stratification in patients with acutely decompensated HF.

Suggestions/Considerations for Clinical Practice/Public Health Initiatives

1. Measurement of predischarge BNP or NT-proBNP during an HF hospitalization can be useful for establishing postdischarge prognosis.

OUTPATIENT MANAGEMENT OF HF

Biomarker assessment in the outpatient management of HF is of benefit for diagnostic and prognostic applications, whereas therapeutic applications remain under active investigation. The diagnostic and prognostic utility of biomarker assessment has been addressed elsewhere in this document and is based on a robust evidence base with a high degree of certainty. Where the database is less certain, however, is in the use of biomarkers to guide or support the outpatient management of HF.

Establishing the Premise of Biomarker Assessment as Treatment Target for Ambulatory HF

Since the emergence of biomarkers as barometers of ventricular wall stress and remodeling, which in turn implicate HF status, there has been hope that biomarker-guided therapy might better facilitate not only attainment of optimal doses of evidence-based medical therapy for HF but also improved clinical outcomes. The heterogeneity of patients with HF has made it difficult to comfortably extrapolate the results of rigorously controlled randomized clinical trials to the everyday clinical environment, and the optimal doses of evidence-based therapy cannot be precisely identified for all patient cohorts. In addition, overzealous titration of hemodynamically active medications may result in harm. The use of a biomarker assay to better gauge the adequacy of medical therapy on the basis of modulation of ventricular wall stress might therefore ameliorate the negative consequences of blindly titrating medical therapies to the point of hemodynamic instability and may optimize ideal clinical outcomes in response to lifesaving therapies for HF.

Reducing Risk of HF Through Biomarker Screening and Intervention

The STOP-HF trial (St. Vincent's Screening to Prevent Heart Failure) evaluated the use of BNP as part of a screening program to identify an at-risk population, coupled with a collaborative care program to implement HF prevention therapies. The study evaluated whether this strategy could reduce newly diagnosed HF and preva-

lence of significant LV systolic or diastolic dysfunction. There were 1374 participants with cardiovascular risk factors recruited from 39 primary care practices and randomly assigned to receive usual primary care or screening with BNP testing. Intervention group participants with BNP levels ≥50 pg/mL underwent echocardiography and collaborative care between their primary care physician and specialist cardiovascular service. The intervention group underwent more cardiovascular testing and received more renin-angiotensin-aldosterone system–based therapy at follow-up. The primary end point of new-onset HF was significantly reduced (odds ratio, 0.55; 95% CI, 0.37–0.82; *P*=0. 003).[209] These findings suggest that among patients at risk of HF, BNP-based screening and collaborative care reduced the combined rates of LV systolic dysfunction, diastolic dysfunction, and HF.[210]

Positive Biomarker-Guided HF Trials

One of the first and most provocative efforts at guided therapy for HF was published in 2000 in seminal work done by Troughton et al.[211] In this early natriuretic peptide–guided therapy study, 69 patients were randomized to either continued medical therapy–guided by clinical assessment or NT-proBNP–guided therapy with a target NT-proBNP reduction equivalent to <1700 pg/mL. The clinical assessment was predicated on a defined HF score based on several specific clinical parameters (ie, Framingham criteria for HF including orthopnea, paroxysmal nocturnal dyspnea, third heart sound, and jugular venous pressure) and attainment of an HF score <2. In both arms, a rigorous stepped-care algorithm was incorporated to normalize treatment options between the 2 groups. This was a double-blind study; however, an investigator aware of the treatment assignment was responsible for adjustments in therapy. A multicomponent outcome of aggregate cardiovascular events, including death, was deemed to be sufficiently powered with 37 patients in each group, anticipating a 50% difference in event rates. Fewer clinical events were noted in the BNP group than in the clinical group (19 versus 54; *P*=0.02). Death alone was nearly statistically significant, 1 versus 7 (*P* =0.06). The most important treatment differences in the NT-proBNP group were higher doses of angiotensin-converting enzyme (ACE) inhibitors and loop diuretics and greater exposure to aldosterone antagonists. The accompanying editorial for the Troughton et al landmark study heralded the milestone this work represented but indicated that the entirety of the response could not be pinned on a reduction in filling pressures because higher doses of neurohormonal antagonists likely exert pleiotrophic effects on the ventricle that go beyond reduction of filling pressures and likely target gene expression, redox potential, and compliance.[211a]

These positive data led to a series of investigations addressing larger and more contemporary patient populations and not only the feasibility of guided therapy but the best accompanying strategy. The French Multicenter Randomized Study to Improve Outcomes in HF by Jourdain et al[212] (also known as the STARS-BNP trial [Systolic HF Treatment Supported by BNP]), expanded on the Troughton et al[211] study by including patients treated with β-blockers, a larger study population of 200 patients, and a more aggressive target BNP nadir in all patients of 100 pg/mL. In a mean treatment duration of 15 months, this study was also positive with a reduction in HF-related deaths and hospitalization. Like the Troughton et al study, patients receiving guided natriuretic peptide therapy were on higher doses of ACE inhibitors, but in this study, a similarly higher dose of β-blocker therapy was also attained. Although this was a positive study, it is not clear that the study was sufficiently powered for the prespecified end points.

Neutral Biomarker-Guided HF Trials

Of the several biomarker-guided HF trials failing to reach the prespecified end point, PRIMA (Can Pro-Brain-Natriuretic Peptide Guided Therapy of Chronic HF Improve Heart Failure Morbidity and Mortality?) is prototypical. The PRIMA study by Eurlings et al[213] enrolled 345 patients and targeted discharge NT-proBNP after HF hospitalization or the observed lowest NT-proBNP in the 2 weeks after hospitalization. This more "individualized" approach was intended to minimize overtitration of therapies in patients with persistently elevated NT-proBNP. The primary end point in PRIMA was days alive and out of the hospital. The study failed to show a positive result, with similar outcomes between the 2 arms (*P*=0.49). The trigger for titration of evidence-based medical therapy in PRIMA was a change in NT-proBNP levels of >10% of the individualized baseline and was ≥850 pg/mL. This led to fewer titrations, with only 23% of outpatient visits meeting the thresholds requiring drug titration, and raises the possibility that the threshold biomarker levels triggering evidence-based medical therapy titration were uniformly too high. Nevertheless, the same observations applied as before: Higher doses of ACE inhibitor use were recorded but in this trial without an apparent clinical benefit.

Pivotal Biomarker-Guided HF Trials

The TIME-CHF randomized trial (Trial of Intensified vs. Standard Medical Therapy in Elderly Patients With Congestive Heart Failure) evaluated treatment of HF guided by NT-proBNP levels with clinical assessment.[214] In TIME-CHF, the targeted NT-proBNP level was 400 pg/mL in those <75 years of age and 800 pg/mL in those >75 years of age, and the clinical arm was symptom driven to NYHA class II or better. Importantly, this trial was conducted in older people dichotomized to <75 or >75 years of age to address concerns that higher doses of

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HF therapy might lead to unintended consequences in the older frail patient. The end point was survival free of all-cause hospitalization for HF and quality-of-life assessment. There was no difference in survival free of all-cause hospitalization, and quality of life improved in both the NT-proBNP and clinically guided arms. For the secondary end point, survival free of HF hospitalization, the NT-proBNP arm significantly benefited. Importantly, the benefits noted were seen only in the group <75 years of age. Doses of ACE inhibitors, angiotensin receptor antagonists, and β-blockers were all higher in the NT-proBNP group, and greater use of spironolactone was noted. The group >75 years of age experienced a lesser increase in β-blocker dosing. Of concern, more serious adverse events related to NT-proBNP–guided therapy versus symptom-guided therapy occurred in patients ≥75 years of age (10.5% versus 5.5%) but not in patients 60 to 74 years old (3.7% versus 4.9%). The interaction between age and treatment groups was P=0.01. It is noteworthy that post hoc analyses from the TIME-CHF study included the unexpected observation that biomarker-guided HF care was cost-effective (despite adverse events), regardless of age.[215]

The more recently completed PROTECT study (ProBNP Outpatient Tailored Chronic Heart Failure) pursued this question yet again but used a single center with advanced HF care and targeted an NT-proBNP threshold of <1000 pg/mL.[216] The primary end point was total cardiovascular events. The results were striking, with 58 versus 100 events in the guided therapy versus the standard of care arm. The positive results extended to quality of life,[217] EF, and indexes of LV volume.[218] No dichotomy in outcome was seen in those <75 or >75 years of age.[219] The predominant differences in medical therapy were greater use of aldosterone antagonists and less use of loop diuretics in the guided therapy group. The differences in the use of ACE inhibitors and β-blockers were not significant. Importantly, PROTECT did not fully randomize as an interim analysis, and the results of other contemporary studies prompted the investigators to end recruitment early. As with some other biomarker-guided trials, the study was unblinded, although event adjudication was blinded. The studies completed to date are summarized in Table 3.

Unresolved Questions

This array of clinical trials plus others noted in the meta-analysis by Savarese et al[210] (Figure 2) and the individual patient data pooled analysis by Troughton et al[221] more recently establish the validity and safety of guided therapy as a means to attain optimal doses of evidence-based medical therapy for HF but make it clear that there are insufficient data to date to definitely support guided therapy as a means to improve clinical outcomes. The major questions to be resolved are the following:

Goal natriuretic peptide threshold? A nadir is needed that is sufficiently low that events are reduced or a percent reduction that reflects a more individualized approach, but when in the course of disease is that threshold set?

Augmented medical therapy? As some have opined, if the result is higher-dose therapy with ACE inhibitors or β-blockers, why not prescribe them empirically? Similarly, if greater exposure to aldosterone antagonism is associated with better outcomes, then optimal implementation of the prevailing clinical practice guidelines would prompt use of aldosterone antagonists regard-

Table 3. Understanding the Heterogeneity of Guided Heart Failure Trials

	Age	HFpEF?	Low Target Natriuretic Peptide?	Natriuretic Peptide Reduced Significantly?	Did Natriuretic Peptide Guidance Change Therapy?
STARBRITE	60	No	No	No	Yes
TIME-CHF	77	No	Yes	No	Yes
B'SCAR	76	Yes	Yes	No	Yes
PRIMA	72	Yes	No	No	No
SIGNAL	78	No	No	No	No
Troughton	70	No	Yes	Yes	Yes
STARS-BNP	65	No	Yes	Unknown	Yes
Berger	71	No	Yes	Yes	Yes
PROTECT	63	No	Yes	Yes	Yes

B'SCAR indicates BATTLESCARRED (NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death); HFpEF, heart failure with preserved ejection fraction; PRIMA, Primary Rituximab and Maintenance; PROTECT, ProBNP Outpatient Tailored Chronic Heart Failure; SIGNAL-HF, Swedish Intervention study–Guidelines and NT-proBNP Analysis in Heart Failure; STARBRITE, Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting: Brain Natriuretic Peptide Versus the Clinical Congestion Score; STARS-BNP, Systolic HF Treatment Supported by BNP; and TIME-CHF, Trial of Intensified vs. Standard Medical Therapy in Elderly Patients With Congestive Heart Failure. Reprinted from Januzzi et al[220] with permission from Elsevier. Copyright © 2011, Elsevier Inc.

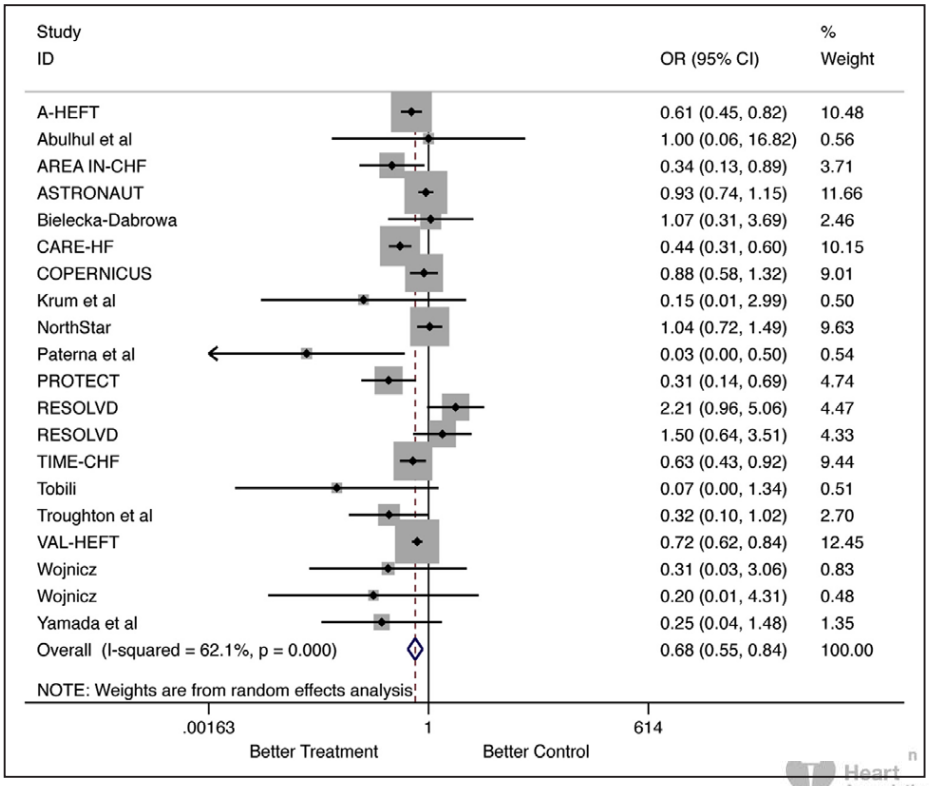

Figure 2. Meta-analysis of guided therapy heart failure trials.
A-HEFT indicates African-American Heart Failure Trial; AREA IN-CHF, Antiremodelling Effect of Aldosterone Receptors Blockade With Canrenone in Mild Chronic Heart Failure; ASTRONAUT, Aliskiren Trial on Acute Heart Failure Outcomes; CARE-HF, Cardiac Resynchronization–Heart Failure; CI, confidence interval; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; OR, odds ratio; PROTECT, ProBNP Outpatient Tailored Chronic Heart Failure Therapy; RESOLVD, Randomized Evaluation of Left Ventricular Dysfunction; TIME-CHF, Trial of Intensified vs. Standard Medical Therapy in Elderly Patients With Congestive Heart Failure; and VAL-HEFT, Valsartan Heart Failure Trial. Reprinted from Savarese et al[210] with permission from the American College of Cardiology Foundation. Copyright © 2014, the American College of Cardiology Foundation.

less of BNP thresholds. The signal associated with less use of diuretics may be more important than previously realized. Observational data have consistently aligned higher-dose loop diuretic use with less good outcomes. Whether this is a risk marker for advanced disease or a risk factor through exaggerated neurohormonal activation remains unresolved but could be operative as the use of biomarker-guided therapy is further explored. Ultimately, there are not prevailing metrics to determine optimal dosing of evidence-based medical therapy at the patient threshold. The use of biomarkers as a surrogate for wall stress represents a reasonable alternative to empirical targeting of historical dosing thresholds achieved in clinical trials.

A signal of harm? It is important that in the quest to optimize clinical outcomes as a function of the attained doses of evidence-based medical therapy, unforeseen consequences can be avoided. This is especially certain in the elderly, who are at risk for falls, cognitive dysfunction, and renal failure as blood pressure, orthostatic hypotension, and cerebral/renal blood flow become affected by higher-dose medical therapy.

Cost-effectiveness? Is the more intensive therapy associated with guided therapy, including extra visits, a reasonable tradeoff for any realized gains?

HF phenotype? The previously completed guided therapy trials did not exclusively limit management to HFrEF. Given the absence of evidence-based therapy for HFpEF, the very premise of guided therapy, that is, titration of evidence-based medical therapy, cannot be accomplished.

Moving Forward: The Next Iteration of Guided HF Therapy

GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure) is a prospective, randomized, controlled, multicenter clinical trial designed to randomize ≈1100 high-risk subjects with HFrEF to either usual care (optimized guideline-recommended therapy) or a strategy of adjusting therapy with the goal of achieving and maintaining a target NT-proBNP level of <1000 pg/mL (Figure 3).[222] Like most studies before it, GUIDE-IT is an unblinded study. The primary end point is

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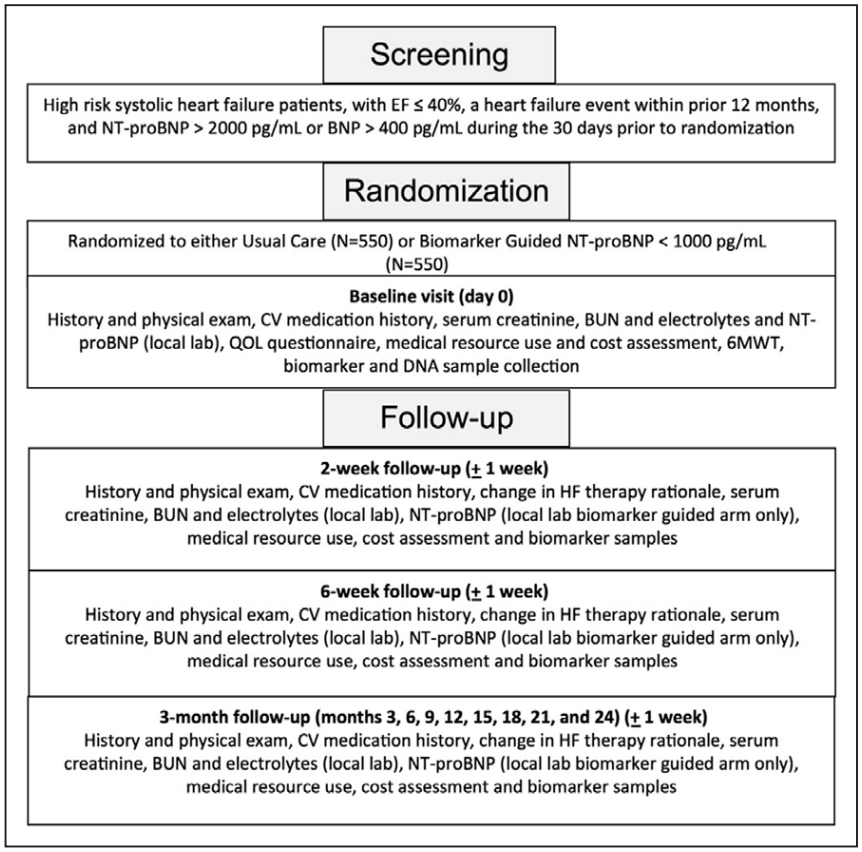

Figure 3. GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure) study design. 6MWT indicates 6-minute walk test; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CV, cardiovascular; EF, ejection fraction; HF, heart failure; NT-proBNP, N-terminal pro–B-type natriuretic peptide; and QOL, quality of life. Reprinted from Felker et al[222] with permission from the American College of Cardiology Foundation. Copyright © 2014, the American College of Cardiology Foundation.

time to cardiovascular death or first hospitalization for HF. Secondary end points include time to cardiovascular death and all-cause mortality, cumulative mortality, health-related quality of life, resource use, cost-effectiveness, and safety. This was to be the first large, adequately powered study addressing the question of biomarker-guided HF therapy and cardiovascular outcomes but has been terminated prematurely because of a lack of difference in the primary outcome between treatment groups.[223] Full details of the trial remain pending, and further analyses with respect to the impact of achieving biomarker targets through serial sampling in important subgroups are currently underway. Although terminated for futility, it is likely that the GUIDE-IT trial results will still be informative. Results from GUIDE-IT are expected to be published in 2017.

As noted by the foregoing comments, the focus of guided therapy in HF has been on NT-proBNP and BNP; that is, natriuretic peptides. Recently, data have emerged evaluating Gal-3, GDF-15, and ST2. Of these newer biomarkers, the most appeal is driven by sST2. The levels appear to vary less as a function of age, sex, body mass index, or renal function. Future efforts may focus on multimarker-guided therapy. Several studies evaluating sST2 have suggested additional utility beyond natriuretic peptides.

Serial assessment of natriuretic peptides in the ambulatory HF model is now limited by some insurance carriers, and full use of this approach may require regulatory and reimbursement adjustments in current delivery models. There remains reasonable interest to more capably deploy evidence-based medical therapy guided by serial clinical assessment, with biomarkers now being one of several strategies. It is evident, however, that many questions remain unresolved. The preliminary data were suggestive, but over time, larger data sets and more rigorous study designs have seen a regression to the mean, with the question now approaching the domain of precision medicine: which patient under which circumstances will respond favorably to a guided therapy approach.

Biomarkers as Therapeutics and the Effect of Natriuretic Peptide Therapeutics on Biomarker Assays

In addition to serving as biomarkers, natriuretic peptides may serve as therapeutics for both HFrEF and HFpEF. Natriuretic peptide levels could be increased either by preventing degradation by neutral endopeptidases such as in the former OVERTURE trial (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) or the more recent PARAMOUNT (Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction) and PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Deter-

mine Impact on Global Mortality and Morbidity in Heart Failure) studies[224–226] or by the exogenous administration of BNP.[224,227–229]

Importantly, the impact of manipulation of endogenous or exogenous natriuretic peptides on measured biomarker levels must be addressed. Specifically, rather than being driven by decompensation of HF or increased wall stress in many cases, BNP_{1-32} levels may increase as a result of the therapeutic effects of neprilysin inhibition or exogenous administration. However, the influence on natriuretic peptide biomarker levels appears not to be universal. NT-proBNP$_{1-76}$ is not a substrate for neprilysin and thus is not directly influenced by the administration of a neprilysin inhibitor. NT-proBNP is also not increased as a consequence of intravenous or subcutaneous therapy.[226] Moreover, patients who achieved NT-proBNP ≤1000 pg/mL in PARADIGM-HF (not as a target of therapy per se) had a lower rate of cardiovascular death or HF hospitalizations compared with those who did not.[230] BNP levels will, however, be affected, but the expected magnitude of increase in BNP_{1-32} concentration after neprilysin inhibition and the durability of increase in BNP_{1-32} concentrations remain unresolved. Whether any other natriuretic assays are affected equally by the effects of neprilysin inhibition is also unresolved.

In the PARAMOUNT study,[224] valsartan/sacubitril significantly reduced NT-proBNP by ≈15% compared with valsartan, and at 36 weeks, valsartan/sacubitril significantly reduced left atrial volume by ≈5% and improved NYHA class compared with valsartan. Whether these effects would translate into improved outcomes will be tested in a large randomized trial (PARAGON-HF [Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction]).

Contemporary Clinical Practice Recommendations[39]

1. BNP- or NT-proBNP–guided HF therapy is of uncertain benefit in clinical practice and cannot be universally advised. There are some data to support the use of serial measurement of biomarkers as a means to achieve ideal doses of guideline-determined medical therapy, but the influence of this approach outside specialized HF centers with highly structured HF disease management programs is unknown.
2. The usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with HF is not well established.
3. The response of NT-proBNP to neprilysin inhibition with concomitant renin-angiotensin-aldosterone system inhibition is associated with positive clinical outcomes but should not be used as a surrogate to guide treatment with an *angiotensin-receptor/neprilysin inhibitor* compound until prospectively acquired randomized data are available.

MANAGEMENT OF HF HOSPITALIZATION

Dynamic Changes in Biomarkers During AHF Hospitalization

Biomarkers play a key role in the diagnosis and initial risk stratification of patients presenting with AHF (Biomarkers and Prognosis in Heart Failure). Hospitalization and treatment for AHF are associated with substantial dynamic changes in hemodynamic and clinical status, which are often reflected in changes in biomarkers of the disease state. In particular, hemodynamic congestion is the most common cause of AHF hospitalization, and most initial therapies (eg, diuretics and vasodilators) are directed at relieving congestion. Of available biomarkers, dynamic changes in natriuretic peptide levels are the best characterized. The primary determinant of natriuretic release from the myocardium is myocardial wall stress,[29] and as myocardial wall stress decreases during successful HF therapy, natriuretic peptide levels fall. These changes in natriuretic peptide levels appear to be related to general improvements in hemodynamic status rather than to the mechanism of action of specific treatments, having been observed with diuretics, vasodilators, and inotropes. Decreases of natriuretic peptide level by 25% to 40% are typically seen during successful in-hospital AHF therapy.[124,162,165,177,231–235]

cTns are also frequently elevated at the time of initial AHF hospitalization (Biomarkers and Prognosis in Heart Failure), even in the absence of overt clinical ischemia such as acute coronary syndromes.[25,236] Troponin changes during AHF therapy have been consistently observed, with most patients having gradual decreases in troponin levels over the course of hospitalization, although the clinical implications of these changes are less clear.[172,177,185–187,234,237] Differences in the sensitivity of various assays have generally complicated interpretation of troponin values in the setting of AHF, although persistently elevated or rising troponin values seem to be associated with greater risk.

Other biomarkers with relevance to HF include sST2 and Gal-3, both of which are felt to reflect myocardial remodeling. Although ventricular remodeling is a continuously ongoing process, the time course of clinically evident changes in ventricular structure or function is typically weeks to months. It is therefore not surprising that biomarkers reflecting remodeling are generally less associated with dynamic changes than hemodynamic markers such as the natriuretic peptides. However, sST2, the ligand for IL-33, is also a mediator of end-diastolic wall stress and inflammation. Hence,

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dynamic changes in sST2 levels during short-term treatment of AHF have been described, and a drop in sST2 levels by at least 20% relate to improvement in subsequent outcomes.[182,183] Gal-3 is also associated with myocardial fibrosis and remodeling but appears to change less dynamically with clinical changes during AHF therapy, suggesting a limited role during acute hospitalization.[238,239]

Biomarkers of Renal Function and Kidney Injury During HF Hospitalization

Changes in renal function during AHF therapy have been a subject of substantial interest and controversy. Initial observational data demonstrated that worsening of renal function (typically defined as a ≥25% decrease in glomerular filtration rate or an increase in creatinine by ≥0.3 mg/dL) during AHF therapy occurs in 20% to 40% of patients with AHF and is generally associated with adverse short- and long-term outcomes.[240,241] A formalized framework for understanding these "cardiorenal syndromes" has been developed, proposing 5 specific subcategories that differ in pathophysiology and clinical implications.[242] Most relevant to the current topic is type I cardiorenal syndrome, in which acute worsening of cardiac function leads to acute renal dysfunction or injury.[243] Although there has been significant focus on changes in creatinine, it is increasingly clear that modest increases in creatinine in the setting of effective decongestion therapy for AHF are not necessarily associated with worsened outcomes.[244–247] There has been significant interest in developing biomarkers that might distinguish acute kidney injury from transient changes in renal function associated with decongestion therapy. Cystatin-C is a marker of glomerular filtration rate that is not affected by body mass or protein intake and may be more sensitive to changes in renal function than creatinine. However, recent data do not suggest that cystatin-C is superior to more traditional measures such as blood urea nitrogen and creatinine in risk stratification in AHF.[248,249] Several markers have been identified that are more specific for renal tubular injury, including urinary and serum neutrophil gelatinase-associated lipocalin, kidney injury molecule 1, N-acetyl-β-D-glucosaminidase, and IL-18.[196,250] Although these tubular injury markers generally appear to be more sensitive and to occur earlier than changes in serum creatinine, their implications in terms of specific clinical interventions remain uncertain.

Biomarkers During Hospitalization and Risk of Postdischarge Events

In theory, biomarkers measured during inpatient treatment could be used to inform decisions about the timing of hospital discharge and the required intensity of postdischarge follow-up. As with other clinical scenarios in HF, the majority of these data have focused on the natriuretic peptides. Observational data clearly demonstrate that the relationship between elevated natriuretic peptide levels at the time of AHF presentation and the level at discharge is closely associated with subsequent risk.[251] Fewer data are available on the relationship between changes in natriuretic peptide levels during HF hospitalization and subsequent events. Early observational studies in single-center cohorts identified either absolute discharge natriuretic peptide levels or the relative decrease in natriuretic peptide during hospitalization as being predictive of postdischarge outcomes.[162,165] Although there are substantial variations among specific studies, generally values of natriuretic peptides at the time of hospital discharge have been found to be more predictive of postdischarge events than earlier values (or the change in values) that occur during hospitalization. Similar data from the ESCAPE study (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) identified discharge BNP as among the most predictive variables for postdischarge outcomes.[252] Natriuretic peptides have also been shown to predict longer-term outcomes after hospitalization. In an analysis of >7000 patients in the OPTIMIZE-HF registry, admission BNP, discharge BNP levels, and the relative drop in BNP (ratio of discharge to admission BNP) were predictive of 1-year mortality or rehospitalization, but the best performance was in models using discharge BNP levels.[146] Although these observational data on natriuretic peptide levels during hospitalization and risk suggest the possibility that clinical decisions (eg, more intense hospital treatment, the timing of hospital discharge, or the time of hospital follow-up) could rationally be made on the basis of natriuretic peptide testing, these hypotheses have not been tested in a randomized controlled trial. A prospective trial to test a strategy of usual care versus a natriuretic peptide target (30% reduction in NT-proBNP) in decision making about hospital discharge is ongoing.[253]

Contemporary Clinical Practice Recommendations[39]

Hospitalized/Acute

The usefulness of BNP- or NT-proBNP–guided therapy for acutely decompensated HF is not well established.

Suggestions/Considerations for Clinical Practice/Public Health Initiatives

1. BNP or NT-proBNP concentrations collected after treatment may be useful for prognosis in hospitalized patients with acutely decompensated HF.

POTENTIAL APPLICATION OF BIOMARKERS IN CLINICAL TRIALS AND QUALITY ASSURANCE PROGRAMS

Biomarkers have increasing important applications in randomized clinical trials. Biomarkers have been used as part of clinical trial enrollment criteria to more reliably establish that enrolled subjects have HF, to establish disease severity, to selectively identify a higher-risk population for enrollment, to provide insights into mechanisms of action, as clinical trial end points in early-phase trials, and to evaluate differential efficacy or safety. In addition to their role in clinical trials, biomarkers can be used in a variety of ways for HF performance improvement, quality assurance, and prevention programs.

Establishing a Diagnosis of HF for Clinical Trial Enrollment

Biomarkers have increasingly been used as components of enrollment criteria of clinical trials in acute and chronic HF to better ensure that the subjects enrolled actually have HF, moving beyond potentially more subjective variables of clinical symptoms and physical examination findings as the sole basis for HF diagnosis for trial entry. Assays for BNP and NT-proBNP have been increasingly used in randomized clinical trials to establish the presence and severity of HF. Clinical trials for both acute and chronic HF have used BNP and NT-proBNP to confirm a clinical diagnosis of HF requiring levels above a diagnostic cut point for patients to meet entry criteria. In general, BNP and NT-proBNP values are reasonably correlated, and either can be used in clinical trials. BNP and NT-proBNP are useful to support clinical trial enrollment criteria for the diagnosis or exclusion of HF in the setting of chronic ambulatory HF or the ED/hospital setting of AHF. Natriuretic peptide testing as part of trial entry criteria is particularly valuable for clinical trials early in the course of AHF when the cause of dyspnea may be not entirely clear. Lower values of BNP or NT-proBNP can effectively exclude the presence of HF, except in the presence of obesity. However, it should be noted that although higher values have reasonably high positive predictive value to diagnose HF, elevated plasma levels for both natriuretic peptides might be the result of a variety of cardiac and noncardiac causes. BNP and NT-proBNP levels may be affected by age, race, sex, body mass index, or comorbidities such as atrial fibrillation. A variety of different levels for natriuretic peptide have been used in different clinical trials, and there are opportunities for better standardization.[4]

Other biomarkers may have a potential role for diagnostic purposes in clinical trials. In the BACH trial, midregional proANP at a prespecified threshold of 120 pmol/L was noninferior to a BNP level of 100 pg/mL for the diagnosis of AHF. The use of both BNP and midregional proANP slightly, but significantly, enhanced the diagnostic performance of BNP. Similar to BNP and NT-proBNP, midregional proANP levels may be affected by age, race, sex, body mass index, or comorbidities such as atrial fibrillation.[144] Confirmatory studies are needed to establish the role of other biomarkers as a diagnostic tool for clinical trial entry and to determine whether they have any potential advantages over BNP and NT-proBNP biomarkers.

Clinical Trial Risk Enhancement

With the increasing availability and use of evidence-based, guideline-directed therapies for HFrEF, event rates for the traditional hard end points of mortality and hospitalization have fallen. Clinical trials have increasingly used certain prognostic variables as components of study entry criteria to select a patient population at higher risk of clinical events to better ensure sufficient powering of the trial. Higher NYHA functional class, lower left ventricular ejection fraction, and recent HF or cardiovascular hospitalization have been used for this purpose. Biomarkers have also been successfully used for clinical trial risk enhancement. In the EMPHASIS-HF trial (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), patients were included only if they had a verified cardiovascular hospitalization in the prior 6 months or if the BNP level was ≥250 pg/mL or NT-proBNP was ≥500 pg/mL in men or ≥750 pg/mL in women.[254] This trial was stopped early as a result of benefit. In the PARADIGM-HF trial, patients were required to have a BNP level of ≥150 pg/mL or NT-proBNP of ≥600 pg/mL or, if the patient had been hospitalized for HF within the previous 12 months, a BNP of ≥100 pg/mL or NT-proBNP ≥400 pg/mL.[225] This trial also was stopped early because of benefit. In the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist), although event rates were below expectation and the prior end point was not met, the subgroup of patients enrolled on the basis of BNP criteria had event rates that met expectations, whereas those patients enrolled on the basis of prior hospitalization did not.[255] Furthermore, for patients enrolled on the basis of prior hospitalization, spironolactone had no effect on the primary composite outcome (HR, 1.01; 95% CI, 0.84–1.21; P=0.92), whereas for those patients enrolled on the basis of elevated BNP levels, spironolactone showed a benefit effect (HR, 0.65; 95% CI, 0.49–0.87; P=0.003; P value for interaction=0.01).[255] Because BNP, NT-proBNP, and Gal-3 have been shown to identify patients with HF at increased risk for rehospitalization, these biomarkers may be useful for trials testing drugs, devices, or strategies for reducing rehospitalization, allowing enrollment of patients at higher risk of these events.

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Insights Into Therapeutic Mechanisms of Action

Analysis of biomarkers within clinical trials may be useful for gaining insights into mechanisms of action by which clinical benefits were obtained. Such studies may also allow more precise evaluation of the experimental therapy on the specific components of the HF molecular mechanisms targeted. Analysis of serial measurements of biomarkers in the HF-ACTION study (Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training) provided insights into whether the impact of exercise in HF on functional status and risk of adverse of events was mediated by reductions in myocardial wall stress, inflammation, and myonecrosis. This study found that plasma levels of NT-proBNP, hs-CRP, or cTnT did not significantly improve at 3 months with a structured exercise training program, even after accounting for baseline biomarker levels. Higher volume of exercise was also not associated with a reduction in serial levels.[256] Findings from this study challenge the hypothesis that exercise training improves commonly evaluated cardiovascular biomarkers in patients with chronic HF.

The RELAX-AHF study (Relaxin in Acute Heart Failure) examined the effects of serelaxin in patients with AHF. In this study, serelaxin improved 1 of the 2 primary end points, dyspnea measured with a visual analog scale to day 5, but did not affect the Likert scale at 6, 12, and 24 hours and did not reduce the rate of cardiovascular death or HF readmissions to day 60 or days alive and out of the hospital through day 60. However, the prespecified safety end point of the trial, all-cause 180-day mortality, was significantly reduced by serelaxin administration.[257] It was not readily apparent from the trial the mechanisms by which 180-day mortality could be reduced by this intravenous vasodilator infused over a limited duration of time. In a biomarker analysis of RELAX-AHF,[234] serelaxin resulted in favorable changes in markers of cardiac (hs-cTnT), renal (creatinine and cystatin-C), and hepatic (aspartate transaminase and alanine transaminase) damage and of decongestion (NT-proBNP), suggesting that this agent was resulting in faster decongestion and prevention of organ damage, providing a plausible mechanism for the improvement in 180-day survival.

Analysis of biomarkers in the PARADIGM-HF trial, which compared the angiotensin receptor neprilysin inhibitor LCZ696 (400 mg daily) with the ACE inhibitor enalapril (20 mg daily) in 8399 patients with HFrEF, provided additional insights into the effect of treatment on the clinical progression of HF in surviving patients. LCZ696 led to an early increase in BNP but a sustained reduction in other biomarkers of myocardial wall stress and injury (NT-proBNP and troponin) compared with enalapril.[225] These biomarker findings paralleled the clinical findings for HF disease progression, including the fact that fewer LCZ696-treated patients required intensification of medical treatment for HF (P=0.003) or ED visits for worsening HF (P=0.001). They also had 23% fewer hospitalizations for worsening HF (P<0.001) and were 18% less likely to require intensive care (P=0.005). In addition, worsening symptoms of HF were consistently less common compared with the enalapril group. The reduction in HF hospitalization with LCZ696 was evident within the first 30 days after randomization, paralleling the rapid change in biomarkers. Because troponin release reflects ongoing myocardial injury (possibly related to increased wall stress) and even small increases in the levels of troponin reflect a higher risk of disease progression in HF, these biomarker-based findings suggest that this may account for the more effective prevention of the clinical progression of HF by LCZ696 than enalapril. These findings also provide further support for the use of this new therapeutic approach to replace the current use of inhibitors of the renin-angiotensin system in chronic HF.

Clinical Trial End Points

Selecting end points for clinical trials is critical. First, it is important for the success or failure of the trial in terms of determining efficacy and achieving approval of the therapy by regulatory agencies. Second, it has important implications for effectiveness, economic value, and translation into clinical practice. Clinical trials to demonstrate clinical efficacy and safety along with supporting regulatory approval require clinical end points such as mortality, morbidity, and, in some circumstance, functional status.[258] When it comes to phase III trials, biomarkers are not viewed as acceptable surrogates for clinical outcomes by regulatory agencies.[258] However, clinical trials in earlier phases of drug or device development to support proof of concept, to demonstrate dose responsiveness, or to provide preliminary evidence of safety and efficacy may use biomarkers as end points to reflect manifestations of disease pathophysiology. Certain phase II trials have selected on-treatment levels or reductions in BNP or NT-proBNP as primary end points. Other existing or emerging biomarkers may be useful and allow evaluation of the specific HF molecular mechanisms being targeted by the experimental intervention.

In addition, some biomarkers such as troponin, serum creatinine, cystatin-C, and hepatic transaminases can be used as indicators of safety.[259–262] Troponin has been used to detect evidence of myocardial injury with established or emerging inotropic agents. In the RELAX-AHF study, increased troponin, serum creatinine, cystatin-C, or hepatic transaminases were associated with a higher risk of 6-month mortality. In addition, larger decreases in NT-proBNP were associated with a lower risk of 6-month mortality. Patients randomized to serelaxin had significantly lower levels of serum creatinine, blood urea nitrogen, and uric acid within the first 5 days after randomization and a lower level of hepatic transaminases within the

first 3 days after randomization compared with patients randomized to placebo.[257] Although favorable effects on laboratory variables were associated with long-term clinical improvement, further study is required to determine whether a single or composite biomarker end point could be used as a safety end point for phase III trials.

Differential Efficacy and Safety in Clinical Trials

Biomarkers have been used frequently in post hoc subgroup analyses of patients enrolled in clinical trials to determine whether the biomarker may be able to identify subgroups of patients with greater or lesser response to therapy or for which there may be different risk-to-benefit ratios. These analyses aim to demonstrate whether a given biomarker can classify patients into distinct subgroups who respond differently to therapy. They may also provide mechanistic insights. In the CORONA study (Controlled Rosuvastatin Multinational Trial in Heart Failure), patients with chronic HF and coronary artery disease were randomly assigned to rosuvastatin or placebo with no significant impact on the primary composite end point. However, it was observed post hoc that those patients with Gal-3 levels less than the median (19.0 ng/mL) appeared to have benefited from statin therapy.[263] These results raised the hypothesis that Gal-3, a biomarker of myocardial fibrosis, might be used to identify a subgroup of patients with HF who would derive benefit from statin treatment.

Quality Assurance Programs

Because HF results in substantial morbidity, mortality, and healthcare expenditures, understanding and improving the quality of health care delivered to patients with HF is imperative. The rates adherence to national performance measures for patients with HF is variable but improving, and certain targeted interventions to improve adherence HF measures have been successful. Biomarkers have a potential role in various aspects of quality assurance programs, including enhancing HF case finding, identifying higher-risk patients for more personalized disease management interventions, and identifying patients at risk for HF for targeted prevention efforts.

Biomarkers can be useful in quality assurance programs by assistance with case finding. BNP-based algorithms have been used to identify patients with HF in the inpatient and outpatient settings to allow concurrent quality improvement efforts. Some quality assurance programs have used screening strategies to identify patients with elevated BNP or NT-proBNP levels for secondary screening. Biomarkers can also be used to identify patients at higher risk for mortality, hospitalization, or rehospitalization. Current guidelines recommend use of HF disease management programs in patients at higher risk of rehospitalizations, and biomarkers may be one of the more effective means to identify such patients.

Suggestions/Considerations for Clinical Practice/Public Health Initiatives

1. In HF clinical trials, measurement of biomarkers may be useful as a component of study entry criteria, in establishing disease severity, and in better identifying an at-risk population to be enrolled.
2. Use of biomarkers for providing mechanistic insights, identifying cohorts of patients with greater or lesser therapeutic responses or safety risks, or targeting certain mechanisms of action in clinical trials may be beneficial.
3. Use of biomarkers for identifying patients with or at risk for HF, establishing disease severity, and stratifying risk can be helpful in quality assurance programs.
4. The use of biomarkers as primary end points in phase III randomized clinical trials as surrogates for clinical outcomes is not well established.

GENOMIC MARKERS: METABOLOMICS AND GENETIC, PROTEONOMIC, AND TRANSCRIPTOMIC MARKERS

Genetic factors likely contribute to the interindividual variation in the propensity to develop HF. For instance, in the FHS, individuals with a parental history of HF are ≈70% more likely to develop HF compared with individuals without a parental history, even after adjustment for conventional risk factors.[264] Although familial clustering may result from both genetic factors and shared environment, the correlation of common substrates for HF (such as LV mass) is much higher between siblings than between spouses sharing a common environment.[265]

Efforts to unravel the genetic determinants of HF have focused largely on cardiomyopathies with mendelian inheritance patterns.[266] This work has led to the identification of a variety of causal mutations responsible for familial cardiomyopathies. Less is known about the genetics of common forms of HF such as that which arises in the background of coronary heart disease or hypertension. For a complex phenotype such as HF, it is possible that a significant heritable component could be attributable to an accumulation of common genetic variants (eg, minor allele frequency >5%) with modest individual effects. The identification of common genetic variation underlying complex traits has been greatly accelerated with the advent of genome-wide genotyping arrays. Genome-wide association studies have identified scores of common variants for many chronic diseases, although the mechanisms explaining these associations are frequently unclear.

HF has proven to be a particularly challenging trait to interrogate with common variant approaches, possibly

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because of its phenotypic heterogeneity. The largest published genome-wide association study for HF was performed by the CHARGE consortium (Cohorts for Heart and Aging Research in Genomic Epidemiology) and involved 20 906 white individuals from 4 epidemiological cohorts.[267] The consortium identified only 1 locus at the genome-side significant *P* value threshold. The index single-nucleotide polymorphism (SNP) at the locus was rs10519210 ($P=1.4\times10^{-8}$, chromosomal region 15q22), which is intergenic between 2 genes, *USP3* (ubiquitin-specific peptidase 3) and *CA12* (carbonic anhydrase XII). This variant was not associated with HF in a black sample (n=2895). Furthermore, replication of this SNP association in a separate study has not yet been reported.

Other efforts to identify common genetic determinants of HF have involved "sub–genome-wide" approaches. The ITMAT/Broad/CARe (IBC) SNP array contains SNPs at ≈2000 genes of predicted importance to cardiovascular disease. Cappola et al[268] genotyped 1590 cases of HF recruited from 2 referral centers and 577 controls. They identified 1 SNP (rs1739843) in the *HSPB7* gene associated with HF in the original sample, as well as in a replication sample. Interestingly, this SNP has also been associated with sporadic dilated cardiomyopathy in a study conducted by a European consortium.[269] *HSPB7* encodes a heat shock protein expressed in cardiac and skeletal muscle. However, the index SNP is in linkage disequilibrium with another gene, *CLCNKA*, that encodes a chloride channel in the kidney, providing an alternative explanation for the connection to HF. Additional resequencing studies have shown that a missense SNP in *CLCNKA* is associated with HF in 3 additional white cohorts.[270] There are even fewer data on the contribution of genetic variation to outcomes in HF. The CHARGE consortium conducted a genome-wide association study of all-cause mortality in 2526 white and 466 black individuals with HF.[271] One SNP in the *CMTM7* gene was associated with mortality, with a value of $P=3.2\times10^{-7}$, just below the prespecified threshold. No replication of that SNP finding is available.

Although interesting for their potential to shed light on mechanisms of HF susceptibility, these studies underscore the limited clinical utility of genetic "biomarkers" of HF at the present time. Even for the most reproducible finding, at *CLCNKA*, the estimated increase in HF risk per copy of the minor allele is modest at 27%.[270] Little is known about the utility of incorporating genotypic information into screening individuals for future HF risk, diagnosing suspected HF, or stratifying risk in patients with established HF.

Genomics is only one of the "-omics" technologies that can be leveraged to identify novel HF biomarkers. Proteomics and metabolomics refer to the global assessment of proteins and metabolites, respectively, in a biospecimen. Clearly, proteins or peptides can be useful biomarkers in a variety of clinical settings, including HF (the natriuretic peptides) and myocardial infarction (troponins). Identification of informative circulating peptides from other pathways with proteomics is an appealing possibility. Nonetheless, proteomic analyses of plasma have inherent challenges resulting from the enormous quantity of proteins and peptides and the vast dynamic range of concentrations represented (up to 6 orders of magnitude).[272]

A recent proteomic study by Mebazaa and colleagues[273] used mass spectrometry with upfront selection of only a single amino-terminal peptide per protein to reduce the complexity of the starting sample. Starting with 10 cases of acutely decompensated HF and 10 controls, the investigators identified 49 candidate markers, including known markers such as NT-proBNP. Targeted assays were developed for 27 of these candidates and applied to an additional 267 samples. The investigators identified a novel candidate, quiescin Q6, levels of which were ≈50% higher in patients with acute decompensated HF compared with controls or those with stable HF. Areas under the receiver-operating characteristic curve for diagnosing HF (in patients with dyspnea) exceeded 0.85. The investigators also demonstrated that expression of this protein was increased in several animal models of ventricular overload or HF.

Metabolomics platforms quantify levels of smaller molecules, including amino acids and their derivatives, carbohydrates, lipids, organic anions, and other molecules.[272] Circulating metabolites may be the substrates or products of biochemical reactions. Thus, the metabolome (or entire profile of metabolites) may respond more briskly to environmental or physiological shifts than proteins; this is certainly true when metabolites are compared with the genome, which is essentially fixed. Moreover, there are far fewer circulating metabolites compared with circulating peptides, by several orders of magnitude. Metabolomic profiles can be generated in a targeted (typically several hundred metabolites) or an untargeted (thousands of peaks) manner with either mass spectrometry or nuclear magnetic resonance.

Interest in the use of metabolomics to study HF has been spurred in part by the growing recognition that HF is accompanied by a variety of metabolic alterations, including shifts in energy use and systemic insulin resistance. A study of 52 patients with HF and 57 controls demonstrated differences in pseudouridine (modified nucleotide), 2-oxoglutarate (tricarboxylic acid cycle), 2-hydroxy 2-methylpropanoic acid, erythritol (a sugar alcohol), and 2,4,6-trihydroxypyrimidine between cases and controls.[274] Another study examined differences in urinary metabolites between HF cases and controls (n=15 and 20, respectively).[275] Urinary acetate and acetone were nominally higher in cases. Furthermore, cases had higher levels of methylmalonic acid, cytosine, and phenylacetylglycine and lower levels of 1-methylnicotinamide (with *P* values ranging from <0.001 to 0.05). Differences in some of these metabolites (including tricarboxylic acid intermediates) could reflect alterations in energy metabolism, as noted above.

On the other hand, small sample sizes and lack of replication are important limitations of these early attempts at metabolite profiling in HF. Zheng and colleagues[276] investigated the association of metabolomic profiles and incident HF in 1744 black participants in the ARIC study. After adjustment for both established risk factors, 6 metabolites in a targeted metabolomic screen and 10 unknown metabolites in an untargeted screen were found to be associated with incident HF. Four of the 6 known metabolites were involved in amino acid metabolism: N-acetylalanine, p-cresol sulfate, phenylacetylglutamine, and pyroglutamine. The other 2 were prolylhydroxyproline (a dipeptide) and erythritol. After further adjustment for renal function, the associations of all 6 of the known metabolites were attenuated, whereas 3 of the unknown metabolites remained associated. These analyses illustrate the potential advantages and disadvantages of untargeted (or unbiased) approaches to biomarker identification. The chemical identification of unknown metabolites can be difficult, and the findings eventually require validation with targeted assays. On the other hand, this process could ultimately implicate previously unsuspected pathways in HF.

The application of proteomic or metabolomic approaches to biomarker discovery in HF is at an early stage. As with genetic studies, few data exist to validate the use of these biomarkers in prediction, diagnosis, or risk stratification in HF. Nonetheless, improvements in platform sensitivity and bioinformatic pipelines should yield novel biomarkers that are unlikely to be identified with traditional, "candidate pathway" approaches.

Suggestions/Considerations for Clinical Practice/Public Health Initiatives

1. The routine use of genotyping or metabolomic profiles for screening, diagnosis, or risk stratification of patients with HF is not well established.

GLOBAL PERSPECTIVE FOR BIOMARKER APPLICATION

The global pandemic of HF is expected to worsen in subsequent decades; thus, expedited development of novel diagnostics and therapeutics and changes in the delivery of such therapies are needed. The content of this statement illustrates the rapid and remarkable growth in the understanding of biomarker testing in HF. Such biomarkers might be leveraged for better care of patients with HF, but obstacles exist.

The Challenges of Translating Biomarker Science to Bedside Use

With rapid evolution in biomarker science, inevitable challenges have come up with respect to the optimal means by which a candidate HF biomarker might be evaluated and ultimately used. Once a robust HF biomarker has a potential role identified, there are obstacles to overcome before widespread use of the biomarker occurs. Such obstacles include cost, regulatory barriers, and challenges in optimal evaluation and deployment of biomarkers.

Although natriuretic peptides and hs-troponins are in use in many countries, they are not as widely adopted as they might be, often because of financial concerns. This is particularly an issue in countries with public and private payers. It is the responsibility of the in vitro diagnostics industry to develop more economical methods for biomarker measurement to disseminate potentially valuable technology more widely.

From a regulatory perspective, the US Food and Drug Administration and other governing bodies must use more realistic assessment assays. Lack of regulatory guidance with respect to the development and deployment of newer biomarkers may slow down the pipeline of newer assays; a close working relationship between regulators, industry, and clinical trialists is crucial. In addition, more streamlined assessment of how the use of HF biomarkers might augment therapeutic strategies for the diagnosis is crucial; with evolution in both areas, considerably greater adoption of biomarker testing into clinical practice guidelines and more widespread clinical use would be expected to occur.

We argue that a new paradigm for HF biomarker research is needed. The current state of HF biomarker research is that of exponential gains in information that far exceed the ability to contextualize findings.[4] This is due in part to inconsistent research methodologies, restricted study sizes, and lack of clinical correlation.[1] To facilitate a robust and rapid transition for a biomarker from bench to bedside, a call has recently been made for more standardized methods for analyses.[4] Study sizes must be increased significantly, and studies should have participants that reflect populations in which biomarkers might be tested. Statistical assessment of biomarkers should be rigorous, emphasizing not only discrimination and calibration (when appropriate) but also the value of a biomarker relative to clinical information with the use of reclassification assessment.[5] To overcome the inevitable challenges of study size and cost, collaborative consortia providing economy of scale are critically necessary. Such consortia should work collaboratively with governmental funding agencies, nongovernmental sources of support, and industry partners. It is through this form of collaboration that the translation of biological information to a clinically actionable result can be achievable in a timely fashion.

Thanks to high-throughput technologies, novel biomarkers are being identified at a high rate, and an inevitable rise in the number of publications on HF biomarkers has been seen.[2] It is our position that the quality of studies and how such studies might be able to lead to changes in how care is delivered should be heavily emphasized.

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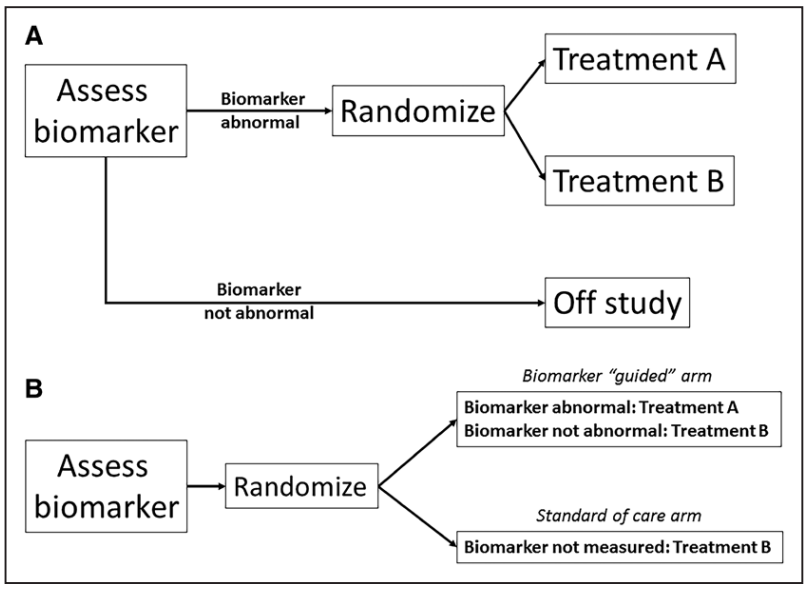

Figure 4. Different means by which biomarkers may be used to alter therapy choices in HF.
A, Biomarker enrichment. Only those patients with an abnormal biomarker receive therapy. This is the design used in the recent PARADIGM-HF trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure). **B**, Biomarker strategy. Those patients with an abnormal biomarker receive standard care but delivered in an intensified fashion with the goal of reverting the biomarker to normal. This is compared with those with a lower biomarker who receive standard care alone. This is the design of the ongoing GUIDE-IT HF trial (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure).

Diagnostic studies of novel biomarkers have the proportionally lowest "bar" to surmount in terms of acceptance and the face-value validity of result. The landmark studies of BNP and NT-proBNP for the identification or exclusion of HF are examples of such trials[75,87,223]; both biomarkers have highest-level support in recent clinical practice guidelines from the United States for this application,[39] reflecting reasonably widespread acceptance. Both BNP and NT-proBNP are highly sensitive for the presence of HF and are unlikely to be replaced as the gold standard for the diagnosis. Nonetheless, concerted efforts to develop other biomarkers to improve the diagnostic specificity of the natriuretic peptides and to diagnose specific aspects of HF (eg, diastolic myocardial abnormalities[98]) in an accurate, cost-effective way would be welcome.

The majority of recent studies of HF biomarkers have focused on prognostic value. These studies have typically emphasized the role of such markers in patients with symptomatic HF, and several novel biomarkers for predicting risk for a broad range of complications, including death, have been identified. Although it is reasonably simple to demonstrate that a biomarker predicts risk for hazard beyond clinical variables or other biomarkers, variability in the quality of these studies is common. Furthermore, given the significant number of studies describing prognostic biomarkers, we suggest that it is critical to consider how such knowledge can be leveraged to improve the risk predicted by the biomarker. In other words, can a biomarker result lead to further diagnostic testing, modification of therapeutics, and cost-effective improvement in patient outcome? Is this prognostic biomarker actually predictive? If not, the value of such a biomarker is substantially reduced. Studies translating prognostic value to clinically actionable information in patients with symptomatic HF are thus highly encouraged. Ultimately, this "therapy guidance" is potentially the most robust future application of prognostic biomarkers.

Strategies for biomarker-based therapy guidance are depicted in Figure 4. One approach is to select therapies only in those patients with an elevated concentration of a prognostic biomarker. Recent large-scale clinical trials such as PARADIGM-HF have used such an enrichment approach.[225] The advantage of this design is that it emphasizes intervention in higher-risk subjects and evaluates whether such risk may be mitigated. The obvious drawback is that it does not evaluate therapy in biomarker-negative subjects. Another design is the use of biomarkers in a "strategy" design. In this approach, patients are treated with standard clinical approaches for HF therapy but with a parallel goal to target lower biomarker concentrations below a prognostic threshold. This strategy presupposes that a biomarker concentration reflects a remediable signal (eg, myocardial remodeling) and assumes that therapies for HF reduce biomarker concentrations and, if such a reduction occurs, that an improved risk profile results.

As noted, an important area to emphasize for study is the use of prognostic biomarkers to assist in the recognition of apparently well patients at higher risk for HF onset and to guide therapy to reduce such risk. Studies of natriuretic peptides, sST2, hs-troponins, and other biomarkers in apparently well subjects suggest that the ability exists to identify asymptomatic molecular signatures of myocardial disarray. Such signals ultimately manifest as symptomatic HF, but few data are yet available on whether such risk can be mitigated. Ultimately, the means by which biomarkers may be used for "precision" techniques to improve the outlook for patients across the entire spectrum of HF (from at risk to advanced symptomatic disease) must be accelerated because the incidence and prevalence of this highly morbid diagnosis are growing rapidly.

FOOTNOTES

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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*Modest.

†Significant.

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Role of Biomarkers for the Prevention, Assessment, and Management of Heart Failure: A Scientific Statement From the American Heart Association

Sheryl L. Chow, Alan S. Maisel, Inder Anand, Biykem Bozkurt, Rudolf A. de Boer, G. Michael Felker, Gregg C. Fonarow, Barry Greenberg, James L. Januzzi, Jr, Michael S. Kiernan, Peter P. Liu, Thomas J. Wang, Clyde W. Yancy, Michael R. Zile and On behalf of the American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology; Council on Basic Cardiovascular Sciences; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Epidemiology and Prevention; Council on Functional Genomics and Translational Biology; and Council on Quality of Care and Outcomes Research

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