

Editorial

Do Biomarkers Deserve High Marks?



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It seems that the moment of truth for any blood test is if the results can answer the critical questions we all struggle with: What's wrong with the patient? How severe is the difficulty? Tell me what I, as a clinician, should do next? Indeed, biomarkers typically have four main clinical uses:¹ (1) diagnosis, (2) risk stratification, (3) guidance in the selection or titration of therapy in patients with known clinical features of disease,² and (4) screening for preclinical disease.³ So is there a "CBC" or "PSA" for heart failure (HF)? The development of commercially available point-of-service assays for biomarkers, particularly troponins and B-type natriuretic peptide and its inactive N-terminal fragments, has led to a dramatic increase in the number of studies evaluating the potential clinical use of measurement of these biomarkers for all four of these clinical uses and particularly for HF. Biomarkers, along with other diagnostic modalities, may also be used to elucidate pathophysiologic processes, but they are not without limitations, since clinical features are a result of deviations in the dynamic equilibrium between risk factors, precipitating factors, and the body's ability to defend, repair, compensate, and respond to these factors.

The ability of any diagnostic modality, including biomarkers, to enhance the quality and efficacy of clinical care depends on several factors, including pretest probability, sensitivity and specificity, cost, benefits, risks, patient preference, and alternatives (such as continued observation, or proceeding to another test or empirical treatment). Particularly important is the fact that these tests are largely the results of simple blood draws. Problematic,

however, is an error in the test that results in clinical interventions that can actually be harmful, such as the prescription of aggressive diuretic doses in a patient who has "stable" congestive HF with high B-natriuretic peptide levels. Indeed, the pretest probability of the disease requiring clarification needs to be integrated with the test result to determine a revised post-test probability. Bayesian analysis combines these data mathematically to determine a precise probability. An important assumption in the Bayesian model is that a test adds new additional information above and beyond what is already known. Diagnostic studies are most useful when they have the ability to change a probability across a decision-making threshold so that it alters the clinical management of the patient.⁴ However, for many conditions, the precise threshold that should guide clinical decision making has not yet been determined. Important principles to consider when evaluating and applying the results of diagnostic studies include: (1) Are the results valid? (2) What are the results? (3) Will the results help me in caring for my patients?⁵ Brain natriuretic peptide (BNP) is one biomarker that has been shown to meet these important principles and enhance the quality and efficacy of care in HF.

BNP results in cost savings in the diagnosis of HF. When randomized clinical trials explored a diagnostic strategy, guided by BNP to aid in the diagnosis of HF in patients presenting to the emergency room with shortness of breath, the group that was randomized to have BNP evaluated spent a shorter time in the hospital at lower cost with no increased mortality and morbidity.

In one single-blind study of 452 patients,⁶ point-of-service BNP in the emergency room decreased the rate of hospitalization by 10%, reduced the median length of stay by 3 days, and reduced the mean total cost of therapy by 1800 dollars with no adverse effects on mortality or the rate of re-hospitalization for HF.

Increasing evidence suggests that BNP is also useful in asymptomatic screening, risk stratification, and cost reduction. In the Framingham Offspring Study, when BNP was evaluated in asymptomatic middle-aged individuals, the investigators found that even small elevations of BNP were independently predictive of mortality, HF, atrial fibrillation, and stroke over a mean follow-up period of 5 years.³ When screening for asymptomatic left ventricular systolic dysfunction, BNP testing seems to be cost-effective (less than 50,000 dollars per quality-adjusted life years gained) when used in a population with a HF prevalence of at least 1%.

The use of biomarkers to guide therapy is affected by comorbidities. For example, BNP levels in hospitalized patients are often affected by renal function and obesity.⁷ Therefore, the management of HF using BNP would require that it be measured with renal function and with consideration of body mass index. In the outpatient setting, the STARS-BNP study showed that titrating therapy to BNP levels <100 pg/mL reduced the composite primary end point of

mortality and hospitalization due to HF compared with guideline-directed therapy;⁸ however, not all studies have demonstrated that changes in BNP levels are associated with improved outcomes.⁹ Currently, from an economic perspective, data are insufficient to determine whether regular assessment of BNP is cost-effective for outpatient titration.

As the field of biomarkers continues to evolve, it is increasingly clear that a panel of biomarkers may add incremental value in the management of HF. For example, when BNP and troponin (a marker of myocardial necrosis) are both elevated in HF, mortality risk increases 12-fold compared with those with both undetectable cardiac troponin I and lower BNP.¹⁰ Therefore, incorporating a multi-marker approach in the routine evaluation of heart patients should allow clinicians to more accurately identify high risk patients who may derive benefit from intensive management strategies.

Biomarkers may be used as a package or a strategy. For example, integrating echocardiography with BNP has been shown to improve the diagnosis of HF in the emergency room (Fig. 1).¹¹ In patients presenting with shortness of breath, when BNP is below 100 pg/mL, HF is unlikely (<2%), and it is useful in ruling out HF with a negative predictive value of >95%. When the BNP is >500 pg/mL, HF is very likely (95%); very high levels are associated with a positive

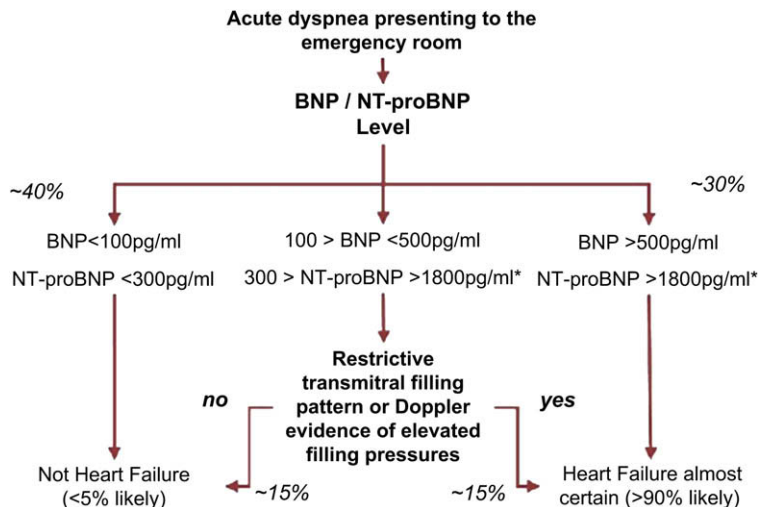


Fig. 1. Combining BNP and echocardiography for diagnosis. Algorithm for integrated use of B-type natriuretic peptide levels and echocardiography for diagnosis of acute heart failure. *Use of age stratified values for amino-terminal pro-B-type natriuretic peptide (NT-proBNP) provides more accurate test performance: <50 years, use NT-proBNP >450 pg/mL; 50 to 75 years, use NT-proBNP >900 pg/mL; >75 years, use NT-proBNP >1,800 pg/mL.¹⁵ (From Troughton RW, Richards AM. B-type natriuretic peptides and echocardiographic measures of cardiac structure and function. *JACC Cardiovasc Imaging* 2009;2(2):216–25; with permission.)

predictive value of >85%. A restrictive transmitral Doppler pattern more accurately differentiates acute HF from noncardiac causes of shortness of breath when BNP is between 100 pg/mL and 500 pg/mL (the intermediate or “grey” zone). The accuracy for early HF diagnosis is improved by up to 30% in patients presenting with acute shortness of breath.¹² Integrating BNP with echocardiography has also been used to more accurately estimate left ventricular filling pressures.¹³ Although BNP is associated with increased left ventricular end-diastolic pressure, the relationship is modest and depends on the clinical scenario. In contrast, the accuracy of tissue Doppler in the estimation of left ventricular filling pressures is better validated. Combining both BNP and tissue Doppler should, therefore, provide more value. Several studies have demonstrated that the addition of tissue Doppler to BNP levels significantly increases the ability to identify high-risk patients, including mortality and readmission (Fig 2). This is one example showing how biomarkers can be combined with other modalities to provide more powerful risk stratification in HF.

Biomarkers are not without limitations, and the assays have inter- and intra-individual variability. These limitations, therefore, make it important that these results are interpreted in the context of clinical history, physical examination, and bedside tests, such as 12-lead EKG and chest roentgenogram. Occasionally however, biomarkers may have incremental value regardless of the pretest probability. For example, in a patient who has shortness of breath and a very high BNP level,

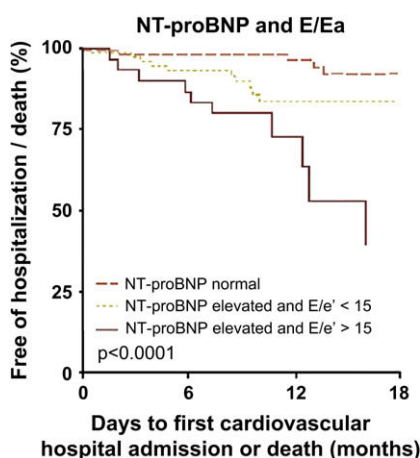


Fig. 2. Combining BNP and echocardiography for risk stratification. (From Whalley GA, Wright SP, Pearl A, et al. Prognostic role of echocardiography and brain natriuretic peptide in symptomatic breathless patients in the community. *Eur Heart J* 2008;29(4):509–16; with permission.)

Box 1

Biomarkers in Heart Failure

Inflammation*†‡

C-reactive protein
Tumor necrosis factor α
Fas (APO-1)
Interleukins 1, 6, and 18

Oxidative stress*†§

Oxidized low-density lipoproteins
Myeloperoxidase
Urinary biopyrrins
Urinary and plasma isoprostanes
Plasma malondialdehyde

Extracellular-matrix remodeling*†§

Matrix metalloproteinases
Tissue inhibitors of metalloproteinases
Collagen propeptides
Propeptide procollagen type I
Plasma procollagen type III

Neurohormones*†§

Norepinephrine
Renin
Angiotensin II
Aldosterone
Arginine vasopressin
Endothelin

Myocyte injury*†§

Cardiac-specific troponins I and T
Myosin light-chain kinase I
Heart-type fatty-acid protein
Creatine kinase MB fraction

Myocyte stress†‡§¶

Brain natriuretic peptide
N-terminal pro-brain natriuretic peptide
Midregional fragment of proadrenomedullin
ST2

New biomarkers†

Chromogranin
Galectin 3
Osteoprotegerin
Adiponectin
Growth differentiation factor 15

* Biomarkers in this category aid in elucidating the pathogenesis of heart failure.

† Biomarkers in this category provide prognostic information and enhance risk stratification.

‡ Biomarkers in this category can be used to identify subjects at risk for heart failure.

§ Biomarkers in this category are potential targets of therapy.

¶ Biomarkers in this category are useful in the diagnosis of heart failure and in monitoring therapy.

From Braunwald E. Biomarkers in heart failure. *N Engl J Med* 2008;358(20):2148–59; with permission.

echocardiography is indicated even in the absence of abnormalities on physical examination and bedside investigations.

The Braunwald classification of biomarkers¹ for HF divides them into seven categories, including markers of inflammation, oxidative stress, extracellular matrix remodeling, myocyte injury, myocyte stress, neurohormones, and renal dysfunction (**Box 1** and the Preface to this issue). Dr. Braunwald included newer biomarkers in a separate class in the *New England Journal* article. In this issue of *Heart Failure Clinics*, Dr. Braunwald has assembled a panel of experts in this field to discuss biomarkers included in this classification. These experts demonstrate that biomarkers singly, as a panel of markers, or in conjunction with other modalities such as echocardiography are an important addition to the clinical armamentarium and should be a valuable adjunct to a thorough history and clinical evaluation at these points of care. Biomarkers serve to enhance the quality and efficacy of clinical care by helping with triage and risk stratification. In particular, they allow cost reduction of medical care by leading to early initiation of highly effective therapeutic strategies that reduce the risk of complications of the disease process, by reducing or even eliminating the need for other more expensive diagnostic studies, or by establishing an alternative diagnosis that does not require hospitalization.¹⁴ In our opinion, biomarkers do deserve high marks!

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