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EDITORIAL COMMENT

Biomarkers in Heart Failure

Does Prognostic Utility Translate to Clinical Futility?*

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Cardiac biomarkers are tools that should aid the physician in one or more of the following: diagnosis and subsequent risk stratification, risk stratification for secondary prevention, guiding selection of therapy, and, finally, in some cases, serving as a target for therapy. Since the advent of the successful rapid uptake of natriuretic peptide levels for use in heart failure, there have been a flurry of new biomarkers, most of which are being touted as prognostically important in heart failure. Growth differentiating factor (GDF)-15 is the latest marker that shows promise in this area. Growth differentiating factor 15 has a number of overlapping pathways in the heart that make it a good choice for evaluation. While not normally expressed on cardiac myoctyes, GDF-15 does appear to be up-regulated in response to experimental pressure overload in the mouse model of cardiomyopathy (1). In gene-targeted mice, GDF-15 has mitigating effects on hypertrophy, apoptosis, and remodeling (2). In the present study, which included a cohort of 455 patients with congestive heart failure (CHF), GDF-15 remained an independent predictor of mortality, with additive value to New York Heart Association functional class, ejection fraction, and amino-terminal pro–B-type natriuretic peptide (BNP) levels.

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Although this study was well conceived, one must ask the question whether a marker that provides independent prognostic information beyond established clinical and biochemical parameters automatically places it in the queue as the "next great biomarker" for CHF. To rise to the top means outperforming the only currently accepted biomarker family for heart failure, the natriuretic peptides. Although there are many caveats concerning the use of natriuretic peptides in heart failure, at this time they are clearly the king of the castle, a measure by which every other pretender or contender will have to be compared.

What Makes Natriuretic Peptide Levels the Standard Bearers for Heart Failure Markers?

First and foremost, a useful biomarker for CHF should have clear pathophysiological relevance to the onset and progression of the disease. They should be used not only to help diagnose the underlying condition or exacerbation of the condition, but the markers should be able to be manipulated by treatment. More than that though is that its prognostic capabilities should lend themselves to clinical decision-making. The only markers that approach this bar thus far are the natriuretic peptides. Indeed, natriuretic peptides (both BNP and NT-proBNP) are excellent adjuncts for ruling in and ruling out heart failure in the setting of acute dyspnea (3,4). Their pathophysiology is so directly related to the results of increased stress on the myocyte that exogenous administration of BNP (nesiritide) is effective treatment for decompensated CHF (5). But the notion that prognostic importance of natriuretic peptides is evolving into clinical tools for decision-making is not only exciting but helps chart the pathway for new players in the field. There are a number of areas where one is beginning to translate the prognostic utility of natriuretic peptides into clinical utility.

Acute Setting

In patients presenting to an emergency department with dyspnea, natriuretic peptide levels clearly aid in the diagnosis of heart failure. The REDHOT (Rapid Emergency Department Heart Failure Outpatient Trial) study suggested that the BNP level in patients presenting with dyspnea was much more important prognostically than any other feature, including the perceived severity of heart failure by the attending physicians (who were only told that the BNP level was >100 pg/ml) (6). Extrapolating results from REDHOT suggests that patients' presenting with CHF whose BNP level is <200 pg/ml may not gain any advantage by admission unless an associated comorbidity like pneumonia of acute coronary syndrome is present. The fact that 11% of patients were admitted with BNP levels <200 pg/ml in this study suggests that in a country where 75% to 90% of heart failure in the emergency room is admitted, millions of dollars in cost savings could be made simply by discharging patients from the emergency department with low BNP levels after appropriate treatment; REDHOT also suggested that patients with BNP levels above 600 pg/ml might do better with admission but this must be substantiated by larger studies.

Hospitalized Patients With Acute Decompensated Congestive Heart Failure (ADHF)

While there are many standard biomarkers that are prognostic in the patient admitted with ADHF (blood urea

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nitrogen, creatinine, and uric acid, to name a few), natriuretic peptides bring unique qualities to the hospitalized setting. B-type natriuretic peptide, for instance, has a "wet" and "dry" component, "wet," which correlates to the amount of volume overload in the patient. As the half-life of BNP is only 20 min, decongesting the patient will lead to a fall in BNP levels of 50 to 75 pg/ml/h (7). Recently, this "wet" BNP level has been found to consist of "altered forms" of BNP; these may include both the precursor, proBNP, as well as smaller fragments, which, while measured by current natriuretic peptide assays, do not activate the natriuretic peptide receptors, thus being termed "junk BNP" (8,9). Future work may make it possible to have specific assays for both the "dry" and the wet" BNP.

Whereas BNP levels in the emergency department may dictate admission, level of care, and type of treatment, the lack of fall in BNP levels with treatment (especially early on) is a poor prognostic sign that may signal additional measures may be necessary (10,11). In my own practice, patients admitted for ADHF receive initial parenteral diuretic therapy. But after 1 to 2 doses, if there is worsening of renal function, an inadequate urine output, and either no change or an increase in BNP levels, patients are often begun on aggressive vasodilator therapy with a drug like nesiritide.

Because declining BNP levels in the hospital can help delineate a patients "optivolemic" volume status, it makes sense that the lower the natriuretic peptide level is at discharge the better off the patient will be. Would we sacrifice an extra day or more hospitalization, ensuring the BNP level was at optivolemic status, if this would cut down the 30-day readmission rate? The answer is likely to be yes, yet this data is currently lacking at the present time. Nevertheless, the prognostic importance of natriuretic peptide levels in the hospitalized patients with ADHF should lead to better treatment algorithms in hopes of reducing hospital readmission.

Ambulatory CHF Patients

In the ambulatory setting, we have less information than we would like on how a prognostically important biomarker like BNP or troponin would influence outpatient therapy of heart failure. In patients who appear at clinic in a decompensated state, BNP levels are almost always increased. Whereas the individual variation of BNP levels may be high, McDonald's group (12) recently found that a 56% increase in values went along with decompensation.

Although drugs like angiotensin receptor blockers are associated with an improved prognosis in patients with CHF along with decreasing natriuretic peptide levels (13), the cause and effect has not been fully elucidated. Several studies have suggested that outpatient titration of drugs by the BNP level leads to improved prognosis (14,15). However, this is still a slippery slope, as evidenced-based utilization of life-saving medicines should still be given as per guideline recommendation.

What about using prognostic biomarkers to help risk-stratify patients for cardiac resynchronization therapy (CRT) and/or implantable cardioverter-defibrillator (ICD) insertion? The fact that up to one-third of patients who receive CRT are nonresponders behooves us to look closely at other criteria for placement of these devices. While studies are few with small numbers of patients, the data thus far suggest the following:

- Elevated BNP levels predict sudden death and ICD firing (16,17).
- Elevated preimplant BNP levels *may* identify CRT responders, although those with lower BNP *after* implant have better outcomes (18,19).
- In CRT responders, BNP levels fall (20).

At present, BNP is not part of guidelines for ICD or CRT implantation. Certainly more work should be done in this area.

Limitations of Natriuretic Peptide Testing

Although natriuretic peptide testing is certainly part of everyday practice, there are clear limitations to its usefulness. In the emergency department, grey zone numbers (100 to 400 pg/ml) need clinical correlation. Caveats such as obesity and renal dysfunction need to be accounted for. For screening, it is still unclear as to what levels will provide added sensitivity or specificity to traditional testing (21).

The Future: GDF-15 and Beyond

Most of the currently used biomarkers were developed from studies of known proteins. Although this approach led to significant advances, advances in protein display and identification technologies permit characterization of global alterations associated with various disease states. Thus, the field of proteinomics is emerging as a novel approach for discovering biomarkers that directly relate to the pathophysiology of disease. These diseases processes are understood to be related to changes in protein expression or modification. Therefore, accurate detection of these alterations in disease states by proteomics might enable us to identify potential drug targets, as well as biomarkers to monitor disease progression or modification. The next steps for GDF-15 is to further define cutoff values, assess how the marker tracks with changes in treatment and clinical status, and, finally, to see if it can be an aid in clinical decision-making.

In conclusion, the study by Kempf et al. (22) in this issue of the *Journal* demonstrates a promising new biomarker in the prognosis of patients with heart failure. Further study will be needed to show whether this prognostic utility will translate into clinical utility or futility.

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