Use of Biomarkers in the Management of Heart Failure
Are We There Yet?

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“What gets you into trouble is not what you don’t know, it’s what you know for sure, that just ain’t so.”

Yogi Berra

Although the advent of clinical practice guidelines and disease management strategies for patients with heart failure has resulted in dramatic overall improvements in patient care, the day-to-day management of individual patients with heart failure remains challenging. As one example, current heart failure practice guidelines recommend that doses of angiotensin-converting enzyme inhibitors and β-blocker should be titrated to the levels used in clinical trials. Although this “one dose fits all” approach is entirely logical (and necessary) from the standpoint of clinical trial design, it is not necessarily logical in the management of individual heart failure patients, in whom body mass (and hence drug disposition) may range from morbidly obese to cachectic. The above example, which is emblematic of the types of problems that clinicians face when they try to adapt and individualize practice guidelines for their own patients, raises the broader question of how clinicians should individualize management strategies for heart failure.

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In the current issue of the Circulation, Anand and colleagues report on changes in brain natriuretic peptide (BNP) and plasma norepinephrine (PNE) levels in patients who were enrolled in theValsartan Heart Failure Trial (Val-HeFT). The authors measured BNP and NE levels before randomization and during follow-up in approximately 4300 patients enrolled in the trial. As with other studies that have examined therapeutic responses in relation to levels of circulating neurohormones, Anand and colleagues observed that the relative risk of having an event was significantly higher for those patients in whom the baseline BNP and NE levels were significantly elevated. The authors also found that BNP was a more sensitive predictor of morbidity and mortality than NE. However, the salient finding in the study by Anand and colleagues was that changes in BNP and NE levels tracked therapeutic outcomes. That is, morbidity and mortality were least in those patients with greatest decrease in BNP and NE levels, whereas the morbidity and mortality were greatest in those patients with the greatest percent increase in BNP and NE levels during the course of the trial. Thus, these data from a large scale well-designed clinical trial provide compelling evidence that changes in neurohormonal levels over time are associated with changes in morbidity and mortality in heart failure patients. One of the important issues raised by these findings is whether clinicians should use changes in levels of biomarkers, such as PNE and/or BNP, to guide heart failure management. Given the potential importance of this concept, it is useful to review the emerging role of biomarkers in treatment of patients with heart failure, as well as to discuss whether we now have sufficient information to use biochemical markers as a means to guide heart failure management.

What Constitutes an Ideal Biomarker to Guide Heart Failure Management?

For a biochemical marker to be considered useful in guiding the management of patients with heart failure, at least 2 conditions must be satisfied. The first and most obvious set of conditions relates to the technical measurement of the biomarker. An ideal biomarker should be highly sensitive and specific for heart failure and should be able to be reproduced and standardized across different clinical laboratories. Furthermore, the inherent error in the technical measurement itself (coefficient of variation) should be sufficiently low over the entire spectrum of values for the biomarker, so that small changes in the level of the biomarker reflect true changes in the clinical status of the patient. Finally, the assay should be relatively easy to perform and analyze so that the information is readily available to the clinician while the patient is still in the treatment area. The second, more difficult set of conditions relates to issues regarding the biological validity of the biochemical marker. In a perfect world, changes in the level of a biomarker for heart failure would accurately reflect changes in the patient’s clinical status, as well as changes in the patient’s prognosis. That is, optimizing the level of the biomarker through changes in therapy should translate into improved, meaningful clinical outcomes. Furthermore, the benefits obtained with the use of an ideal biomarker should be applicable to men and woman of all ages, and of all different racial backgrounds. One could also make the argument that the ideal biomarker should make “physiological sense”; that is, there should be a pathophysiological basis for believing that changes in the level of the biomarker are linked to changes in the clinical status of the patient.
**Do We Currently Have an Ideal Biomarker for Guiding the Management of Heart Failure Patients?**

Although the heart failure literature is rife with examples of circulating biochemical markers that predict poor outcomes in patients with heart failure, there is far less information regarding the use of biomarkers to predict changes in the clinical status of the patient. Of the myriad of biochemical markers that have been examined, PNE and the natriuretic peptides are the best characterized biomarkers that have been studied in the context of heart failure. However, as will be discussed below, neither of these biochemical markers meets the definition of an ideal biomarker.

Measurements of PNE have been shown to predict survival and the clinical response to treatment with enalapril in the CONSENSUS (COoperative North Scandinavian ENalapril Survival Study) trial, the V-HeFT II (Vasodilator-Heart Failure Trial II) trial, and the SOLVD (Studies On Left Ventricular Dysfunction) treatment and prevention trials.2–4 Moreover, PNE levels were decreased in the treatment arm of SOLVD.4 Despite these auspicious findings with PNE, other studies have raised important concerns about the validity of PNE measurements to track clinical outcomes. In the Australia-New Zealand Carvedilol Heart Failure Trial, carvedilol reduced heart failure admissions only in patients with PNE levels that were below the median.5 Further, in the PRIME II study (the Second Prospective Randomized Study of Ibopamine on Mortality) and the MOXCON study (Efficacy and the Effect of Sustained Release Moxonidine on Mortality and Morbidity in Patients with Congestive Heart Failure), treatment with ibopamine and moxonidine resulted in a significant increase in mortality that was associated with a decrease in circulating levels of PNE.6,7

Plasma natriuretic peptides, including atrial natriuretic peptide (ANP) and BNP are increasingly being recognized as important prognostic markers in patients with heart failure. Nonetheless, the extant clinical literature suggests that ANP levels are less reliable in terms of predicting clinical outcomes in heart failure than are BNP levels. For example, ANP levels did not decrease after treatment with enalapril in the SOLVD prevention study, even though overall hospitalizations were reduced by enalapril.4 In contrast, the Australia-New Zealand Carvedilol Heart Failure Trial showed that carvedilol reduced mortality rates and heart failure admissions in patients with higher baseline BNP levels.5 Treatment with spironolactone resulted in a decrease in BNP levels that paralleled the effects of spironolactone on mortality in the RALES trial (Randomized Aldactone Evaluation Study).6 Smaller single-center studies have confirmed the utility of BNP measurements in assessing clinical outcomes and have shown that changes in BNP levels track clinical outcomes in patients hospitalized for heart failure.9,10 Apropos of the present discussion, BNP-guided treatment for heart failure has been shown to reduce total cardiovascular events, including cardiovascular death and a delayed time to first cardiovascular event when compared with clinically guided treatment in a randomized study.11 Taken together, these data demonstrate a consistent relationship between changes in BNP levels and clinically meaningful outcomes such as death and/or change in patient symptom status. Furthermore, BNP levels are currently available as a point-of-care assay, thus making them clinically available while the patient is in the treatment area.

Despite the many potential strengths of BNP as a biomarker for assessing the effectiveness of heart failure therapy, there are a number of cautionary notes that warrant discussion. In the RESOLVD pilot study (Randomized Evaluation of Strategies for Left Ventricular Dysfunction), initiation of metoprolol CR/XL was associated with an initial rise in BNP levels compared with placebo, despite a trend toward a decrease in mortality in the treatment arm.12 Thus, it will be important to determine whether changes in the levels of BNP can be used to monitor all therapeutic approaches in heart failure, or whether instead changes in BNP levels will only track clinical outcomes for a subset of therapeutic approaches. Indeed, it may be unrealistic to expect a single biomarker to track all of the different pharmacotherapeutic and device-driven advances that are currently evolving in the field of heart failure. Further, at the time of this writing, it is unclear whether the measurement of N-terminal BNP (the biologically inactive precursor form of BNP) or the biologically active secreted form of BNP will be most useful for guiding heart failure therapy. Whereas the longer half-life and increased stability of N-terminal BNP may be desirable for predicting prognosis, the shorter half-life of the biologically active fragment of BNP may be more useful for tracking changes in patient clinical status. Finally, proprietary commercial interests have led to the development of different antibodies that detect different amino acid residues on the BNP molecule, thus raising the potential problem of standardizing BNP assays across different laboratories.

**Biomarkers in the Management of Heart Failure: Are We There Yet?**

In the current issue of *Circulation*, Anand and colleagues1 properly conclude that “strategies to reduce neurohormonal levels for mortality and morbidity are at present premature and not justified.” On the basis of the arguments delineated above with respect to the characteristics of the ideal biomarker, it is clear that we have not yet achieved the level of sophistication that is necessary to reliably use biomarkers to optimize clinical care for patients with heart failure. This statement notwithstanding, the important study by Anand and colleagues does provide the scientific basis for the notion that biomarkers may one day help in optimizing heart failure management, particularly for those patients who are not doing well on standard forms of therapy. One might envision that clinicians could use combinations of different biomarkers that reflect different aspects of the disease process to optimize multiple facets of patient care, or use genetic biomarkers to provide an optimized pharmacogenomic approach, or perhaps even use screening biomarkers to select specific types of therapies (eg, use of immunoadsorption for patients with autoantibodies against the β1-receptor). Whereas our colleagues in oncology have long championed the use of biomarkers to individualize therapeutic strategies for their patients, it has only been recently that cardiologists have
began to use biochemical markers to guide the patient management, such as the use of troponin levels for high-risk acute coronary syndromes. Although it is always difficult to make accurate predictions about future therapeutic approaches in heart failure, the wealth of emerging clinical data suggests that it is increasingly likely that clinicians will one day have sufficient information to use biomarkers to facilitate and optimize the care for their heart failure patients. However, before we take this next step, biomarker-guided strategies will have to be validated extensively in long-term epidemiological studies, as well as in clinical studies that demonstrate the added value of this type of approach over and above the clearly established benefits that are provided by our current best approach to the management of heart failure. The potentially good news for clinicians and their patients is that these types of studies are either being planned or are presently ongoing.

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References

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