Contemporary Challenges in Translating Biomarker Evidence Into Clinical Practice*

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With acute heart failure (AHF) being one of the most common and costly reasons for hospitalizations in the U.S., establishing the clinical utility of B-type natriuretic peptide (BNP) and aminoterminal pro–B-type natriuretic peptide (NT-proBNP) testing has been an important advance in this area. With thousands of papers published, a decade of clinical experience, and perhaps the only heart failure biomarker to have its own guidelines endorsement (1), the bar has been set very high for newer biomarkers to demonstrate their potential uses in the management of patients with AHF.

The importance of atrial natriuretic peptide and adrenomedullin as compensatory neurohumoral pathways has been extensively described in the literature over the past few decades. Animal models have identified both measurements as potent hormones with vasodilatory and natriuretic properties (2,3). In patients with heart failure, both play important roles in maintaining cardioenal homeostasis. Both have been isolated in cardiovascular tissues, and their detectable increase in plasma levels has long been described in the setting of heart failure (4,5). In fact, both hormones have even been developed as vasodilator drugs for therapeutic use (6). Although measurements have been limited to research-based assays and were hindered by their relatively short half-lives and instability, plasma levels of both hormones have been associated with adverse long-term outcomes (7,8).

In this issue of the Journal, the BACH (Biomarkers in Acute Heart Failure) trial investigators (9) tested the hypothesis that measuring 2 stable mid-region fragments of pro–hormones for atrial natriuretic peptide (MR-proANP) and adrenomedullin (MR-proADM) can provide incremental diagnostic value in the detection of AHF and prognostic value in patients presenting with acute dyspnea at the emergency department. The BACH trial followed a winning formula of contemporary biomarker studies by completing a large multicenter study design led by world-class investigators, performing sophisticated statistical analyses, and achieving the pre-specified end points to claim significance. In the era of evidence-based medicine, such a well-conducted study provides important insights and is greatly appreciated. At the same time, results of the BACH study may illustrate emerging challenges facing the translation of new research findings into clinical practice in the era of broad adoption of BNP/NT-proBNP testing. The issue in contention is whether demonstration of more appropriate diagnosis of AHF (by adding MR-proANP in subsets) and better prediction of mortality (by adding MR-proADM) can adequately translate into better patient management and clinical outcomes.

Addition of MR-proANP to diagnose AHF. The ability to improve the diagnostic certainty for detecting AHF has been the primary indication for BNP/NT-proBNP testing. It is, therefore, no big surprise that in the BACH trial, there was impressively tight concordance between measurements of MR-proANP and measurements made by commercially available BNP or NT-proBNP assays. As prior studies have questioned the utility of measuring atrial natriuretic peptide because of its instability and wide variability, this “noninferiority” finding in itself is an important illustration that new assay technologies can refine the measurement of a specific peptide to meet a specific purpose. In other words, the quest to distinguish differences among various types of natriuretic peptide tests has now revealed more similarities than differences. As different fragments of natriuretic peptides are being targeted for assay development, a new issue has emerged that is completely independent of whether MR-proANP can provide equivalent diagnostic accuracy. The ranges of measurements are different between various natriuretic peptides (and to a lesser degree among multiple commercially available assays measuring the same peptide). Currently, different values are already being reported for patients cared for at different institutions or locations of care where various assays (BNP or NT-proBNP) are being used. Providing yet another type of natriuretic peptide test would
simply add to the confusion. Hence, in terms of clinical applications, harmonization of these test results may be necessary to avoid unintentional errors in interpreting the results.

The ability to provide incremental diagnostic certainty with a multimarker approach is an attractive concept. The potential for MR-proADM to provide additional insights has been suggested by its ability to predict long-term risk incremental to that of NT-proBNP (10,11) but equivalent to that of BNP (12) in patients with chronic heart failure. Although the prognostic value of MR-proADM was not reported in this paper, the investigators provided elaborate analysis to illustrate the potential incremental diagnostic information with the addition of MR-proADM to BNP and NT-proBNP. While many impressive p values were presented, these analyses made an important assumption that clinicians were rigid in interpreting BNP or NT-proBNP values with pre-defined cutoff values without taking into account potential confounders that may adjust their interpretations. Therefore, whether lowering the perceived BNP cutoff to a level optimal for obese patients may provide the same diagnostic accuracy as adding MR-proADM to BNP needs to be examined. Similarly, whether addition of NT-proBNP to BNP in the “gray zone” can yield similar findings as adding MR-proADM to BNP remains to be explored. Interestingly, the diagnostic accuracy of BNP testing in the BACH trial was lower than that previously reported in the BNP (Breathing-Not-Properly) trial at the same cutoff value of 100 pg/ml with the same assay (74% vs. 83%, respectively) (13). This appears to be due to slightly lower specificity of the test performance in the BACH study population. Although the precise reasons for such difference were not elaborated, this lower accuracy may also favor the addition of MR-proADM to improve decision statistics. Therefore, in reviewing the data from the BACH trial, demonstration of direct improvement in clinical outcomes by enhancing diagnostic accuracy with the addition of MR-proADM, although promising, remains somewhat lacking.

Addition of MR-proADM to predict adverse outcomes in AHF. The BACH investigators (9) reported the incremental prognostic value for MR-proADM in the same population for both short-term (30-day) and long-term (90-day) outcomes. It is interesting to note that the strongest signal for MR-proADM lies in its ability to predict mortality (both all cause and cardiovascular related), and not in other end points such as rehospitalization or revisits (in which the number of events are much higher). The strength of this prediction was highest at short-term follow-up, when the number of events was relatively low (only 35 deaths, with 23 cardiovascular related, at up to 30 days) and appeared to be confined to patients in the highest quartile of MR-proADM. Furthermore, the incremental prognostic information for MR-proADM within patients with AHF was shown only for all-cause mortality and not for other events. In fact, BNP appeared to provide a stronger predic-

REFERENCES


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