Editorial

Is There an Optimal Time or Method to Obtain BNP Levels?

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Brain or B-type natriuretic peptide (BNP) was first identified in humans in 1989.[1] It was shown to be elevated in patients with heart failure (HF) in 1990,[2] with the ventricles quickly identified as the primary source.[3] In 2002, a landmark study illustrating the utility of BNP whole-blood or plasma levels as an aid in the diagnosis of acute HF changed the PubMed landscape forever.[4] Since then, there has been an explosion of literature describing the virtues and limitations of assessing BNP or N-terminal proBNP (NT-proBNP) levels for screening and diagnosis, or prognostication in patients with HF. However, current application is mainly limited to obtaining a level for the purposes of screening and diagnosis. This is reflected in both the current ACC/AHA/HFSA and ESC guidelines for the management of HF, which advocate (class I recommendation) obtaining a BNP/NT-proBNP measurement to establish a diagnosis in acute and non-acute settings.[5,6]

Despite the wealth of data demonstrating the prognostic implications of elevated BNP/NT-proBNP, there remains a lack of clarity on application of these levels beyond the initial diagnosis. The ACC/AHA/HFSA guideline recommendation for obtaining a level pre-discharge (or an additional level to evaluate relative change during the hospitalization) for post-discharge prognostication is more equivocal (class IIa), even stating "the prognostic value of a pre-discharge value or relative changes does not imply the necessity for serial and repeated biomarker measurements during hospitalization".[5] Coupled with the results of studies arguably failing to demonstrate improvement in HF outcomes using a BNP-guided approach to longitudinal management,[7–9] it remains unclear whether obtaining additional or serial BNP/NT-proBNP levels is warranted to establish prognosis, especially in the absence of recurrent hospitalizations. Therefore, major questions regarding optimal use of BNP/NT-proBNP levels remain.

First, when is the best time to obtain a level, especially if only one level is to be obtained? Data clearly show that elevated BNP/NT-proBNP levels obtained at any time point during a hospitalization are predictive of increased mortality or re-hospitalization longitudinally. Most studies have assessed levels collected upon admission or discharge. Importantly, in studies that have compared both admission and discharge (or pre-discharge) levels, discharge BNP or NT-proBNP has consistently been a stronger predictor.[10–13]

Second, if additional levels are obtained beyond a baseline, when are they indicated and how should they be interpreted? It is well established that relative changes over time in BNP/NT-proBNP levels also confer prognostic information. In the patient hospitalized for HF, achievement of incremental reductions in absolute and relative NT-proBNP levels is associated with proportionate reductions in the risk of 6-month mortality.[14] Failure to achieve a 30% reduction in NT-proBNP during a hospitalization for acute HF portends poor outcomes,[15,16] however, a conscientious effort to achieve this endpoint was not associated with improved 6-month outcomes in one prospective study.[9] In studies comparing admission, discharge, and relative change in levels, the relative change in BNP/NT-proBNP was usually an inferior predictor. These data question the value of obtaining serial levels.

In this issue of the Journal, two studies report additional findings in this area. Grodin et al[17] analyzed data from a biomarker substudy of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial. This analysis was novel in that NT-proBNP levels were assessed at baseline, 48−72 hours, and more longitudinally at 30 days. Associations between static, absolute, and relative changes to 30-day death or HF hospitalization, and 180-day death, were modeled. Although the analyses suffers from potential risk of multiplicity, all static, short- and long-term absolute and relative changes in NT-proBNP levels were independently associated with 180-day death, whereas static and relative changes at 48−72 hours, but not baseline, were associated with 30-day outcomes. When added to the ASCEND-HF model, static or relative changes in NT-proBNP improved the discrimination for predicting 180-day death. The results suggest that there is incremental value to obtaining serial NT-proBNP levels,

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whether in-hospital or after discharge, for improving risk-stratification.

Kagiyama et al[18] utilized data from the prospective Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure (REALITY-AHF), to examine the incremental predictive value of percentage BNP reduction over clinical variables and discharge BNP. Not surprisingly, relative change during hospitalization was a superior predictor compared with body weight reduction or discharge BNP for 1-year all-cause death and composite of all-cause death and HF hospitalization. Of note, the results were independent of BNP level on admission, which is in contrast to previous studies. Upon stratifying patients based on left ventricular ejection fraction (LVEF), relative change was not predictive of 1-year mortality in patients with LVEF $\geq$ 50%. Again, these results support the incremental value of obtaining an additional BNP level during a hospitalization for HF.

In the context of existing data, the results of these two studies are largely intuitive. Obtaining a natriuretic peptide level, or any other marker of disease severity, once a patient has received some treatment or is in a compensated basal state, would be expected to represent a more accurate indicator of future risk, whereas levels obtained at the time of acute presentation likely reflect short-term risk. Furthermore, obtaining a (single or additional) natriuretic peptide level at discharge or longitudinally may be reasonable to allow for greater understanding of the clinical trajectory of a given patient. Many examples already exist in cardiovascular disease, such as troponin interpretation in ischemic heart disease and serum creatinine in cardiorenal syndrome, where interpretation of a single value can be problematic.

Interpretation of the current and similar studies should take into account some limitations. Complete separation of admission or baseline levels from discharge or relative change levels remains imperfect, despite statistical modeling. In addition, models used to evaluate incremental predictive value of BNP vary in assessed covariates and may have limited generalizability to other patient populations (eg, ASCEND-HF analysis shows increased discrimination based on the ASCEND-HF model).

Finally, pivotal questions remain. How should additional risk-stratification be used in clinical practice? What adjustments should be made based on additional biomarker data if one chooses to obtain it? An important limitation in the BNP/NT-proBNP biomarker data is that it is derived almost exclusively from retrospective evaluation, so cause-and-effect cannot be ascertained. As the study by Stienen et al[9] demonstrated, modifying management to achieve a specific reduction in NT-proBNP level by the time of discharge was not associated with improved outcomes despite the prognostic signals. Therefore, is the incremental prognostic value tied to additional BNP/NT-proBNP levels actionable?

In lieu of future prospective studies directly comparing HF management guided by single threshold value versus relative change targets in BNP/NT-proBNP levels, we may already have the answer: there isn't a specific optimal time to obtain a level. As the data currently show, single or multiple levels obtained at different times, whether in-hospital or not, can provide important prognostic information related to the risk for short- or long-term major clinical events. However, not all patients with HF may need or benefit from this additional data. Therefore, as for all diagnostic tests, if additional data are needed to inform a management decision, the practitioner should determine whether they are interested in short-term or long-term prognostic data, and determine when one level or multiple levels should be obtained. An individualized approach to biomarker utilization may reap benefits for select patients that are difficult to capture when applied in a widespread manner.

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