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EDITORIAL

Serial, Repeated, or Single Measurements of Natriuretic Peptides (BNP or NT-proBNP) in Estimating Cardiovascular Risk: Is It the "Importance of Change Over Time" or "The Past Is Good, But the Present Is Better," or Both, in Clinical Context?

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The contribution of measuring plasma concentrations of natriuretic peptides (NPs) NT-proBNP (N-terminal pro-B-type natriuretic peptide) and BNP (B-type natriuretic peptide) to aid in diagnosis and cardiovascular risk stratification and guide therapy in patients with heart failure has been well studied. The value of such measurements has also been extended to cohorts of patients without heart failure with coronary artery disease and type 2 diabetes,[1,2] although the clinical uptake for risk assessment in patients with type 2 diabetes has been limited so far. Basic to any discussion of the evolving clinical role of NPs is a persisting issue that brings with it some controversy and ambiguity for the clinician: does a single point-in-time measurement of NP provide actionable prognostic and risk stratifying information or is serial NP sampling over time better suited to address this task? Because disease activity changes over time and is variable between patients and within the same patient, repeated NP measurements would be expected to provide the most actionable approach to patient management. Thus, there are studies demonstrating that changes over varying time periods (increases or decreases from baseline values or relative to specified cut-points) carry high risk stratifying value and aid in reclassifying patients relative to their short- or long-term outcomes.[3–6] However, additional studies support the prognostic value of single samples obtained particularly in the posthospital clinical setting of ambulatory patients.[7–12]

See Article by Wolsk et al.

Highly relevant to this discussion is the importance of the clinical context in which NP measurements are obtained and interpreted. The prognostic value of NPs would be expected to vary whether assessing stable ambulatory low- or moderate-risk patients versus high-risk patients experiencing or recovering from an acute cardiovascular event where intervening factors such as the presence of atrial fibrillation or worsening renal function may confound the interpretation of NP levels. Additionally, the influence of biological and analytical variability needs to be taken into account.[13,14] Therefore, given that any one NP value or particular cut-point value will not apply to every patient cohort

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with differing clinical features, the question may be more properly framed, in a clinical sense, not as which is better but rather what is being asked of the NP data for the patient-specific clinical context and how do these values apply in real-world clinical practice where patient follow-up and testing can be highly variable and not controlled as in the setting of clinical trials.

Here is where Wolsk and colleagues in the current issue of the *Journal of the American Heart Association (JAHA)*[15] add to this discussion by providing their findings from a post hoc analysis of data from the ELIXA (Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment with Lixisenatide) trial.[16] They assessed the prognostic significance of serial (2 samples, baseline and 6 months) NT-proBNP and BNP concentrations in a high-risk ambulatory patient cohort with type 2 diabetes, coronary artery disease, and history of a recent coronary event (within 6 months of study screening). The study intent was to determine the incremental predictive value of 2 serial NP measurements obtained at baseline (time 0) and 6 months and another paired set at 18 and 24 months after study randomization (primary outcome events were determined within a relatively short 6-month period following NP measurements). This was compared with single point-in-time NP measurements obtained at study randomization and at 18 months post randomization (both were considered baseline samples for this aspect of the analysis) with 6-month follow-up intervals for determining primary end point events. The study end point was cardiovascular death or heart failure hospitalization. The study cohort contained 5393 patients with 6911 paired samples (1518 patients contributed 2 separate 6-month observation periods). Six-month follow-up intervals were 0 to 6 months from randomization and 18 to 24 months post randomization for the outcome analyses. A total of 136 outcome events occurred—reflecting 2.5% of the cohort with a majority of events (74%) occurring not unexpectedly in the 0 to 6-month period from randomization.

The study findings importantly support a risk stratifying contribution of NP measurements in a cohort of patients without heart failure and, therefore, an incremental value of the results is the association of NP concentrations with short-term risk in ambulatory patients with coronary artery disease and type 2 diabetes, a high-risk group. The current study shows that a single NP measurement is highly predictive in the context of short-term 6-month follow-up without an absolute necessity of serial sampling. This is consistent with previously reported data from the same ELIXA trial[1] where the median follow-up time was, however, 26 months showing baseline NP levels alone were as predictive of death as a model of combined standard risk factors. Similar findings were reported from the ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) trial.[2] Therefore, having a past NP measurement appears to be of long-term predictive value. The current data of Wolsk et al., however, provide additional granular insight by demonstrating where serial NP measurements are most helpful and that is to refine the predictive value of a prior or baseline NP sample in the short-term measurement interval of 6 months, a valuable contribution to patient management. Further, and importantly, the findings demonstrate that the most current NP value was the most informative overall in predicting the 6-month combined end point—as stated by the authors, "most of the predictive information was provided by the current (most recent) sample." Past NP measurements are good, but from a practical perspective the most temporally available value is likely going to be most actionable in modifying the patient's clinical course. Additionally, study findings suggest that NP values older than 6 months diminish in their predictive capacity, which would seem to have the largest impact on the value of serial measurements. Although serial NP measurements refined the predictive risk and reclassified ~50% of patients in this study, a time frame of 6-month measurement intervals may not conveniently fit with real-world clinical practice and, therefore, if the predictive value of NP measurements declines as the follow-up period extends, it becomes more difficult to interpret and integrate the contribution of NP levels with other clinical factors and ongoing events.

What can we learn from the post hoc analysis by Wolsk and colleagues? Importantly, their findings point to recognizing that we should be proactive, not reactive, in asking what information we want to gather from NP data and then to ask over what time frame do we expect these data to retain their value. If predictive value diminishes over longer time intervals between NP measurements as would be expected with changes in disease activity particularly in higher risk patients, should we then define serial measurements in terms of short-term measurement intervals such as 6 months and differentiate these from more remote longer interval repeat NP measurements that effectively function as new single point-in-time measurements? Although this issue is yet to be resolved, how does it factor into clinical practice? This again leads to the significance of clinical context in that in low-risk stable patients based on standard clinical risk factor assessment it may be sufficient to measure a single baseline NP concentration to determine if the patient is in a higher risk group based on NT level and if not or only modestly elevated above an a priori identified cut-point, then serial values are not likely to be of substantial incremental value. In contrast, in higher risk patients such as the cohort described by Wolsk et al. a baseline NP value would likely support high risk and such

patients are likely to have close follow-up, adjustments in medical therapy or other interventions, or to experience clinical decompensation where short-interval serial NP values can help assess change in risk (for the better, for the worse, or no change). The most valuable NP measurement, however, in this context is the temporally most current NP value, which helps define the "in-the-moment" risk and inform direction for the more immediate plan of management. Finally, the study by Wolsk et al. also reminds us that NPs, whether serial or single point-in-time measurements, need to be viewed in the complete context of other clinical factors and not solely as standalone testing. We still have more to learn regarding the optimal use of biomarkers such as the NPs to identify risk where it was not anticipated clinically and most important to guide modifications in therapy and management based upon biomarker values or changes in biomarker values with the ultimate goal of improving outcomes for our patients with cardiovascular disease and threatening comorbidities.

ARTICLE INFORMATION

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Disclosures

None.

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