Type: Perspective

**Biomarker Testing Considerations in the Evaluation and Management of Patients with Heart Failure: Perspectives from the International Federation of Clinical Chemistry and Laboratory Medicine Committee**

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The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Committee on Clinical Applications of Cardiac Bio-Markers (C-CB) agree on the objective evidence that laboratory biomarkers can provide in the diagnosis of HF and support natriuretic peptides (NP, with BNP and NT-proBNP predominantly available from clinical laboratories) as the most well documented and suitable biomarkers in this regard. We also believe it is important to highlight analytical issues that may affect the clinical interpretation of cardiac biomarkers, including the NPs.1-4 Accordingly, we have listed below the first five of the ten most current laboratory recommendations that clinicians should be cognizant of when ordering NP tests.4  Our aim is to highlight analytic issues of clinical relevance and provide recommendations to help clinicians optimally use NP values with respect to the Universal Definition of Heart Failure. To this end we have listed the recommendations with corresponding text in the Universal Definition of Heart Failure to further clarify these important aspects.

Laboratory Recommendation #1: Clinicians should be aware that different NP assays will provide different concentration values in any given clinical situation. Accordingly, concentrations obtained from different NP assays cannot be used interchangeably. Further, using different NP assays in clinical practice within the same institution is not recommended due to the complex nature of NP processing and cleavage and differences in what assays measure. Extrapolation from one assay concentration to another can be confounding.4

The Universal Definition of Heart Failure states: “In general, both BNP and NT-proBNP values track similarly, and either can be used in patient care settings as long as their respective absolute values and cutoffs are not used interchangeably”.1  The IFCC C-CB still recommends to not interchange assays (i.e., alternating or concurrent BNP and NT-proBNP testing) or even the same assay on different instruments (example central laboratory instrument versus point of care testing). For monitoring purposes, using the same laboratory NP test (both in name and manufacturer) will mitigate analytical confusion which has occurred for other non-standardized assays used in monitoring treatment and follow-up in other conditions (e.g., serum tumor markers in patients with cancer).

Laboratory Recommendation #2: NP assays require extensive analytical characterization prior to implementation in clinical practice.4

While the Universal Definition of Heart Failure does not cover the analytic performance of NP assays, it draws analogy to “the Universal Definition of Myocardial Infarction (MI), where elevations of a circulating biomarker (troponin) are both central to the clinical diagnosis and fundamental to the universal definition itself.”1 Drawing further analogy with the diagnosis of MI, the optimal high-sensitivity cardiac troponin cutoffs for decision making are defined and validated for each assay prior to clinical use. To ensure optimal use of NP assays, the cutoffs used to ‘rule in’ and ‘rule out’ both acute and chronic heart failure should be derived and validated for each assay.

The IFCC C-CB strongly agrees that it is important to emphasize that the close collaboration between the laboratory and clinical community for over two decades has led to the improved analytical and clinical performance as observed today with the high-sensitivity cardiac troponin assays.3 As lower medical decision cutoffs are being proposed for the NP assays, this collaboration and continuing work in the analytical characterization and validation is essential for NP testing.4

Laboratory Recommendation #3: Upper reference limits (URL) for NP assays should be stratified by age and sex. 4

The Universal Definition of Heart Failure states: “A detailed diagnostic algorithm will require specific operational thresholds based on individual natriuretic peptides and assay systems, as well as detailing other clinical features that can affect natriuretic peptide levels (Table 7), but for common clinical purposes, simple thresholds can be established that have sufficient operational accuracy to be incorporated usefully into a universal definition of HF.” and “Thresholds proposed in the table have higher sensitivity and may have lower specificity especially in older patients, or patients with atrial fibrillation or CKD Table 7. Usually, higher cut-off values are recommended for the diagnosis of HF in these patients.” In addition, criteria will vary by age and for screening perhaps by sex as well.4 The IFCC-CB has concerns about how laboratories will identify and correctly flag abnormal NP concentrations as there is tremendous variation in cutoffs (URLs) as detailed by the manufacturers of the NP assays (see Table 1 where ULRs vary by several fold). Presently, no manufacturers list the 35 ng/L cutoff for BNP. Only a few list the 125 ng/L cutoff for NT-proBNP, and only for those age < 75 years. Furthermore, there are no cutoffs in the Universal Definition of Heart Failure for MR-proANP or proBNP. Here, confusion among clinicians concerning the use of clinical decision limits vs URLs for NPs likely exists as well.

Laboratory Recommendation #4: Development of higher order reference methods and commutable standards for BNP and NT-proBNP are strongly recommended, with standardization efforts to consider differences in the NP fragments detected and the impact of glycosylation in different BNP and NT-proBNP assays.4

The Universal Definition of Heart Failure lists 35 ng/L and 125 ng/L cutoffs for BNP and NT-proBNP, respectively, in ambulatory patients. However, there is no international standardization or harmonization for these assays and it is uncertain how close the agreement is between patient results across the various manufacturers. By comparison, because there is also no standardization or harmonization for high-sensitivity cardiac troponin assays, it is recognized that each assay will have its own assay specific cutoffs.3

Laboratory Recommendation #5: Analytical imprecision of NP assays should be improved to allow for refinement of significant clinical changes.4

The Universal Definition of Heart Failure states: “Furthermore, patient-level changes need to be interpreted according to baseline levels; natriuretic peptides are higher during periods of decompensation compared with compensated periods, reflecting dynamic temporal changes.”1 The IFCC-CB has recommended a target coefficient of variation or precision goal of <10% across the analytical range to improve the analytical performance of NP assays while opining that monitoring in the normal range will be helpful, similar to what is recommended for the high-sensitivity cardiac troponin assays.3,4 Further research is warranted to monitor the NP assays in the normal range and understand each assay’s variability/precision, for the optimal application of the Universal Definition of Heart Failure. Also, as seen in Table 1 there is variation on the lower analytical limits and precision of the various NP assays near the URL.

In summary, the IFCC C-CB acknowledges the efforts of the authors of the Universal Definition of Heart Failure and for endorsing an objective biomarker of heart dysfunction, such as the NPs. The IFCC C-CB hopes that closer collaboration will further improve the clinical utility of laboratory testing as it pertains to patients with or at risk for HF.

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Table 1. Analytical characteristics of the NP assays as designated by the respective manufacture. For up to date details please visit the IFCC website: <https://www.ifcc.org/ifcc-education-division/emd-committees/committee-on-clinical-applications-of-cardiac-bio-markers-c-cb/>