

Expert Answers

From the IFCC Committee on Clinical Applications of Cardiac Bio-Markers

CARDIAC Q&A SERIES III: COMMON QUESTIONS ABOUT NATRIURETIC PEPTIDE ASSAY DIFFERENCES & CLINICAL USE

How do I transfer from one natriuretic peptide assay to another and why are they not interchangeable?

The main reason for natriuretic peptide assays not being interchangeable is that all assays for quantification of natriuretic peptides are based on antibody-recognition and thus dependent on epitope sites within the peptide in question. Intact proBNP (1-108) is cleaved to different peptides fragments, often referred to as NT-proBNP, and the C-terminal bioactive peptide BNP. In addition, glycosylated forms circulate in plasma. Different methods display different bindings to the various fragments, and the results between each method cannot be considered interchangeable. A simple requirement to ensure some comparison will require a) specific information on chosen epitopes for the methods in question, b) what peptide fragment is used for calibration, and c) preferably method comparison using for instance Bland-Altman plotting. Most often, there will be an analytical bias between methods, even if they are named the same (for instance NT-proBNP assays). Although assay differences are clearly evident one should note that clinical guidelines currently do not support assay specific cutoffs within NT-proBNP or BNP assays.

Key reference: Goetze JP. B-type natriuretic peptide: from posttranslational processing to clinical measurement. *Clin Chem* 2012 Jan;58:1:83-91

Additional reading: Clerico A, Franzini M, Masotti S, Prontera C, Passino C. State of the art of immunoassay methods for B-type natriuretic peptides: An update. *Crit Rev Clin Lab Sci* 2015;52:2:56-69

Kavsak PA, Lam CSP, Saenger AK, Jaffe AS, Collinson P, Pulkki K, et al. Educational Recommendations on Selected Analytical and Clinical Aspects of Natriuretic Peptides with a Focus on Heart Failure: A Report from the IFCC Committee on Clinical Applications of Cardiac Bio-Markers. *Clin Chem* 2019 Oct;65:10:1221-7

Are there advantages to BNP over N-terminal proBNP?

In clinical heart failure diagnostics, both BNP and N-terminal proBNP measurement is recommended by both the American Heart Association and the European Society of Cardiology. If natriuretic peptide measurement is used as a rule-out marker of heart failure and one is using the assay-specific cut-off value(s), there are no advantages of BNP over N-terminal proBNP measurement. One difference may, however, lie in preanalytical handling of samples, where N-terminal proBNP as a molecule has proven more stable and thus less prone to degradation compared to BNP. NT-proBNP may therefore be easier to handle for laboratories that receive outpatient samples or need to store samples for more than a few hours before analysing them.

Key reference: Omeland T, Hagve TA. Natriuretic peptides: physiologic and analytic considerations. *Heart Fail Clin* 2009 Oct;5:4:471-87

Additional reading: Chien TI, Chen HH, Kao JT. Comparison of Abbott AxSYM and Roche Elecsys 2010 for measurement of BNP and NT-proBNP. *Clin Chim Acta* 2006 Jul 15;369:1:95-9

Mueller T, Gegenhuber A, Dieplinger B, Poelz W, Haltmayer M. Long-term stability of endogenous B-type natriuretic peptide (BNP) and amino terminal proBNP (NT-proBNP) in frozen plasma samples. *Clin Chem Lab Med* 2004;42:8:942-4

🔗 When making a change between BNP and NT-proBNP, how can heart failure progression be assessed if a baseline has not been established or the recommended wait time of at least one month to re-establish a baseline has not been met?

If a laboratory chooses to change from BNP to N-terminal proBNP measurement, or vice versa, there is no simple factor that can be applied. Immunoassays against peptides are dependent on epitopes that are likely to differ between methods. Rather, it is recommended that both assays are used in parallel for some time (1-3 months) before the change can be implemented. Even when different assays are measuring the same natriuretic peptide fragment, they will measure different concentrations, and this is not in a linear manner. Thus, standardisation of assays has not been possible, but harmonization has been proposed. In real-time settings, a few major diagnostic companies have for years dominated the field, and a new method should preferably be compared to one of these.

Key reference: Saenger AK, Rodriguez-Fraga O, Ler R, Ordonez-Llanos J, Jaffe AS, Goetze JP, Apple FS. Specificity of B-Type Natriuretic Peptide Assays: Cross-Reactivity with Different BNP, NT-proBNP, and proBNP Peptides. *Clin Chem* 2017 Jan;63:1:351-8

Additional reading: Goetze JP, Dahlstrom U, Rehfeld JF, Alehagen U. Impact of epitope specificity and precursor maturation in pro-B-type natriuretic peptide measurement. *Clin Chem* 2008 Nov;54:11:1780-7

🔗 During Angiotensin Receptor-Neprilysin Inhibitor (ARNI) treatment, how do BNP and NT-proBNP concentrations differ?

With the introduction of ARNI treatment, neprilysin inhibition has been introduced in heart failure. Neprilysin degrades both ANP and BNP, and inhibition should theoretically increase endogenous ANP and BNP concentrations. However, the neprilysin affinity for BNP is weaker than for ANP. It is likely that other molecules also are responsible for the biological effects. Monitoring of heart failure, therefore, was initially thought to be best pursued using NT-proBNP methods. Initiation of ARNI typically will result in a variable increase in BNP and a reduction of NT-proBNP and new set points will be established for both biomarkers. However, after the initial drug up-titration phase, changes in hemodynamic status will be reflected in changes in both concentrations of BNP and NT-proBNP. Moreover, there are no publications showing that serial BNP measurement for monitoring of heart failure progression or response to therapy is clinically inferior to NT-proBNP monitoring after initiation of ARNI therapy. The prognostic value also seems comparable.

Key reference: Myhre PL, Prescott MF, Claggett B, Felker GM, Butler J, Pina IL, et al. Comparative Effect of Angiotensin Receptor Neprilysin Inhibition on B-type Natriuretic Peptide Levels Measured by Three Different Assays: The PROVE-HF Study. *Clin Chem* 2022 Nov 3;68:11:1391-8

Additional reading: Nishikimi T, Nakagawa Y, Miyamoto S, Kanamori T, Inazumi H, Yanagisawa H, et al. Responses of B-type natriuretic peptide (BNP), mature BNP and proBNP to sacubitril/valsartan differs between responders and non-responders. *Open Heart* 2025 Feb 23;12:1

Myhre PL, Vaduganathan M, Claggett B, Packer M, Desai AS, Rouleau JL, et al. B-Type Natriuretic Peptide During Treatment With Sacubitril/Valsartan: The PARADIGM-HF Trial. *J Am Coll Cardiol* 2019 Mar 26;73:11:1264-72

The information provided above is a brief summary of common questions and answers developed by consensus of the IFCC C-CB committee, however it is important to recognise that greater knowledge and understanding is recommended and can be sourced from the referenced resources and <https://ifcc.org/ifcc-education-division/emd-committees/committee-on-clinical-applications-of-cardiac-bio-markers-c-cb/> including links to detailed papers, podcasts and presentations.