

Serial measurements of natriuretic peptide to assess pharmacological interventions and subsequent impact on cardiovascular risk stratification in heart failure: a precision medicine approach

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Comment on: Zile MR, Claggett BL, Prescott MF, *et al.* Prognostic Implications of Changes in N-Terminal Pro-B-Type Natriuretic Peptide in Patients With Heart Failure. *J Am Coll Cardiol* 2016;68:2425-36.

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Heart failure (HF) is a major worldwide epidemic associated with high morbidity and mortality, with the number of cases expected to increase in line with increasing average life expectancy (1). Progressive advances in medical science have allowed identification of blood-based biomarkers [e.g., B-type natriuretic peptide (BNP), N-terminal prohormone of BNP (NT-proBNP) and troponin] that are able to provide improved prognostic information for patients at risk of or following an HF event. However, their routine use for decision making at times is limited and shows challenging hurdles for precise risk stratification, such as emerging risks being affiliated with sub-clinical myocardial damage for use of troponin and/or inflammatory biomarkers (2) driving researchers to investigate a cocktail of biomarkers to improve risk prediction. Furthermore, cross-validating biomarker characteristics between clinical studies is reliant on comparable use of both study design, as well as collection, analytical and statistical methods for appropriate translations on a population-wide scale (3). Natriuretic peptides (NPs), notably their B-type form, BNP, are perhaps the most widely used of these biomarkers for diagnosis and cardiovascular risk stratification of HF patients (4-6). Prognostic investigations have shown that multiple forms of BNP are indicative of risk in HF, including the parent molecule (7) and its truncated forms (8) as well as the NT-proBNP (9,10).

Clinical trials have previously outlined the beneficial use of NT-proBNP to assess short-term cardiovascular risk in HF patients. For example, the Val-HeFT (Valsartan Heart Failure Trial) and COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trials reported NT-proBNP as an independent predictor of increased risk of death in HF patients (9,10). To extend upon these baseline measurements of NT-proBNP, the Val-HeFT trial also observed relationships between 4-month changes in circulating NP levels and associations with adverse outcome, showing the use of serial measurements of NT-proBNP for risk stratification in stable and chronic HF (9). Recently, Zile *et al.* (11) investigated the use of repeated NT-proBNP measurements to assess how changes in circulating levels are associated with future adverse events, and whether these associations were influenced dependent on the medication treatment strategies employed, with a focus on the new drug; sacubitril/valsartan (LCZ-696). The study investigated 1,942 patients from the PARADIGM-HF [Prospective Comparison of ARNI (Angiotensin Receptor-Neprilysin Inhibitor) with ACEI (Angiotensin-Converting-Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure] trial with circulating NT-proBNP levels measured at baseline and 1 month later after treatment with sacubitril/valsartan (LCZ-696) or enalapril. Changes in NT-proBNP levels showed

least events in patients who measured lower NT-proBNP levels ($\leq 1,000$ pg/mL) at both baseline and 1 month, and conversely the most events for those with higher levels at both measurement points. Interestingly, the authors observed that patients treated with LCZ-696 were almost twice as likely to report a meaningful reduction in NT-proBNP when compared to those administered enalapril, indicating an increased potency on the NP system. These findings highlight that although circulating levels of NP are indicative of patient prognosis, the monitoring of the dynamics and/or kinetics of these processes can provide additional information of clinical benefit.

Clinically, studies such as that by Zile *et al.* (11) indicate the increasing need to develop therapeutic strategies and risk calculations that are tailored and personalised to the patient with a focus on efficiency and precision. In PARADIGM-HF, the use of enalapril and LCZ-696 is focussed on the assessment of their ability to influence NP biology and their resultant effect on the dynamic processing of these cardio-renal protective peptides. In HF, the NP system and levels of BNP are reduced and levels of less physiologically active BNP fragments are increased. Therefore advanced HF may present as BNP deficiency and neprilysin activation is increased enhancing the degradation and hydrolysis of NPs (12). Neprilysin inhibition has been shown to reduce NP degradation (13) and therefore these medicines offer the prolongation of the cardioprotective benefits provided by the presence of these peptides in the circulation. LCZ-696 is a novel ARNI that consists of anionic moieties of neprilysin inhibitor and valsartan, an angiotensin II receptor blocker. LCZ-696 has therefore been shown to inhibit both neprilysin and renin-angiotensin-aldosterone system (RAAS) (12), and reduce degradation of vasoactive peptides such as BNP. However to the contrary, administration of LCZ-696 showed reductions in NT-proBNP levels over a 1-month period, suggesting that NT-proBNP is not a substrate for neprilysin and that it is affected by LCZ-696 through alternative mechanistic interactions. Nevertheless, these results highlight an advantageous use of NT-proBNP as a marker of HF, irrespective of neprilysin inhibition.

Combined efforts to improve prognosis and management of HF rely on therapies, lifestyle changes and palliative care, with biomarkers providing important information on potential repeat hospitalisation or mortality. Whilst many biomarkers are linked to predicting mortality (14), the use of NPs has been repeatedly reported as useful to predict both mortality and rehospitalisation (15,16) whilst also providing key information for more personalised

therapy (17). Zile *et al.* (11) highlighted one beneficial use of NPs in precision medicine showing the use of NT-proBNP for risk stratification where patients who showed a reduction in NT-proBNP concentrations, had a lower rate of mortality of hospitalisation, irrespective of treatment group. To this end we recently reported that additional processed forms of BNP are superior or comparable to NT-proBNP for risk stratification of acute HF patients (8). Although we investigated the three major BNP molecular forms (8), additional forms have also been measured in the circulation (18). The dynamics and kinetics of these degradation pathways are not currently understood and this indicates an importance of both time-dependent and specie-dependent analyses of BNP. Notably, beneficial information from serial sampling of NPs can be extended to other areas of cardiovascular disease with time-dependent changes in NT-proBNP (19) and BNP (20) levels shown to be useful in risk assessment of acute coronary syndromes.

To conclude, Zile *et al.* (11) indicate the beneficial application of serial measurements of NPs for improved prognostic qualities in HF risk management. The 1-month reduction in circulating levels of NT-proBNP was associated with improved outcome and that a contemporary drug, sacubitril/valsartan (LCZ-696), was able to improve this reduction in HF patients, thus suggesting an improvement in prognosis. Further experiments in NPs incorporating serial time-point sampling, as well dynamic and kinetic investigations of degradation pathways, would benefit clinical knowledge for more accurate and precise decisions for HF risk stratification.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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