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EDITORIAL COMMENT

NT-proBNP

The Gold Standard Biomarker in Heart Failure*

Paul M. McKie, MD, John C. Burnett, Jr, MD

remained above 1,000 pg/ml. Again, it should be stressed that the change in NT-proBNP that was prognostic of HF outcomes occurred within the first month. Importantly, more participants achieved this reduction with ARNi therapy compared with enalapril (31% vs. 17%).

The authors are to be congratulated for an important study in HF from both a biomarker as well as a therapeutic perspective. Importantly, the study underscores the use of NT-proBNP as the gold standard for a powerful prognostic biomarker, especially in clinical trials employing a pharmacological agent that inhibits the degradation of natriuretic peptides. A previous report from the PARADIGM-HF trial demonstrated that BNP, the biologically active peptide, as well as cGMP its second messenger, increased following ARNi therapy (12). The differential response of BNP (increased) and NT-proBNP (decreased) in response to ARNi therapy suggests that clinicians be cautious when interpreting the prognostic utility of BNP in the setting of ARNi therapy. In combination with ARNi therapy. Another explanation is related to nonhemodynamic mechanisms leading to greater reduction in humoral simulation of the BNP gene such as reduced endothelin or even improvement in myocardia hypoxia. Another question is whether we would gain more knowledge about treatment efficacy and/or prognosis if we were to employ a multibiomarker strategy involving the entire BNP pathway including proBNP, mature BNP, NEP, and cGMP together with NT-proBNP. From a mechanistic standpoint, knowledge of other natriuretic peptides involved in NEP degradation and inhibition such as ANP and CNP may be of value. Finally, does the current study also strengthen the rationale for the use of NT-proBNP as a regulatory accepted surrogate for HF trials? This could potentially accelerate drug development and approval, perhaps under some circumstances negating the need for expensive and large mortality trials, thus moving more toward the model of development of cancer therapeutics and surrogate biomarkers. The authors are again to be congratulated

Both furin and corin process proBNP to biologically active BNP and nonbiologically active NT-proBNP. BNP mediates its biological actions by binding to its receptor (pGC-A) and activating the second messenger cGMP. BNP is degraded into less biologically active BNP products by the enzyme neprilysin that is highly expressed in the kidney. BNP = B-type natriuretic peptide; cGMP = 3′-5′-cyclic guanosine monophosphate; NT-proBNP = N-terminal pro-B-type natriuretic enzyme.

hypoxia. Measurement of natriuretic peptide now is common as an endpoint in HF trials, and the use of natriuretic peptides for diagnosis and prognosis purposes is guideline supported. Additionally, a large study to evaluate the efficacy of NT-proBNP to guide HF therapy is underway (GUIDE-IT [Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure] trial) (10).

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In this issue of the *Journal*, Zile et al. (11) report findings of the prognostic value of NT-proBNP in the PARADIGM-HF trial. As the authors state, the PARADIGM-HF trial represented an unprecedented opportunity to investigate the prognostic robustness shifting of a neurohumoral profile dominated by the renin-angiotensin-aldosterone system to one more weighted toward the natriuretic peptide/cGMP system with beneficial organ and cellular protective properties secondary to inhibition of NEP, as well as coblockade of AT1R.

The principal objective of the Zile et al. study (11) was to test the hypothesis that the degree of change in NT-proBNP would parallel changes in death and hospitalization. This is an important question in part as the HF community strives to develop surrogate endpoints for HF trials. The investigators defined NT-proBNP levels in a subset of patients in the PARADIGM-HF trial (n = 2,080) and 62% of those subjects (n = 1,292) had an NT-proBNP above 1,000