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EDITORIAL COMMENT

NT-proBNP

The Gold Standard Biomarker in Heart Failure*

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The concept of the heart as an endocrine organ emerged with the discovery of the atrial natriuretic peptide (ANP) by de Bold et al. (1) in 1981, followed later by the discovery of B-type natriuretic peptide (BNP) as an additional cardiac hormone that was structurally similar, but genetically distinct. We now know that the precursor prohormones proANP and proBNP are released from the heart in response to atrial stretch and other hemodynamic and inflammatory stimuli. These prohormones are then processed to their biologically active forms ANP and BNP, and biologically inactive N-terminal proANP (NT-proANP) and NT-proBNP forms. Neprilysin (NEP) is the principal enzyme that degrades the biologically active cardiac natriuretic peptides (ANP and BNP). Importantly, NEP is not involved in the degradation of NT-proANP or NT-proBNP. Biologically, active ANP and BNP bind to the same particulate guanylyl cyclase A receptor (pGC-A), activate the second messenger 3′-5′-cyclic guanosine monophosphate (cGMP) and result in pleotropic actions including natriuresis, vasodilation, suppression of hypertrophy and fibrosis, inhibition of the renin-angiotensin-aldosterone system, and metabolic protective properties.

The importance of the natriuretic peptide system is underscored by the observation that genetic variants of the ANP and BNP genes, which modestly, but significantly, increase circulating levels of ANP and/or BNP, protect against hypertension, structural remodeling of the heart, and metabolic disease (2,3). Reduced bioavailability in early hypertension and asymptomatic heart failure (HF) (Stage B), as well as an increased concentration of biologically inactive molecular forms of natriuretic peptides in advanced HF (Stage C and D, New York Heart Association functional class IV), has laid the foundation for natriuretic peptide-based therapeutics (4-6). The PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial builds upon this foundation with the study of the first-in-class small molecule angiotensin type 1 receptor (AT1R) and NEP inhibitor (ARNi) named Entresto (7). Specifically, the ARNi class antagonizes the deleterious downstream signaling actions of angiotensin II but promotes the cGMP-linked protective actions of the natriuretic peptides, which include, not only ANP and BNP, but also the vasculoprotective peptide C-type natriuretic peptide (CNP), which is the endogenous ligand for the pGC-B receptor. This landmark study demonstrated that ARNi therapy reduced HF mortality and morbidity compared with enalapril, leading to the Food and Drug Administration's rapid approval for the treatment of symptomatic HF with reduced ejection fraction.

Beyond their therapeutic potential, increased production and release of the natriuretic peptides in HF have led to their use as diagnosis and prognostic biomarkers. Indeed, BNP, and more recently NT-proBNP, have become hallmark biomarkers for HF diagnosis and prognosis, being superior to ANP and NT-proANP (8). The superiority of the BNP and NT-proBNP as diagnostic and prognostic biomarkers is related to both hemodynamic, as well as non-hemodynamic, mechanisms that control BNP gene expression (**Figure 1**) (9). Such nonhemodynamic mechanisms for BNP gene expression include stimulation by hormones such as endothelin and angiotensin II, as well as by cytokines and myocardial

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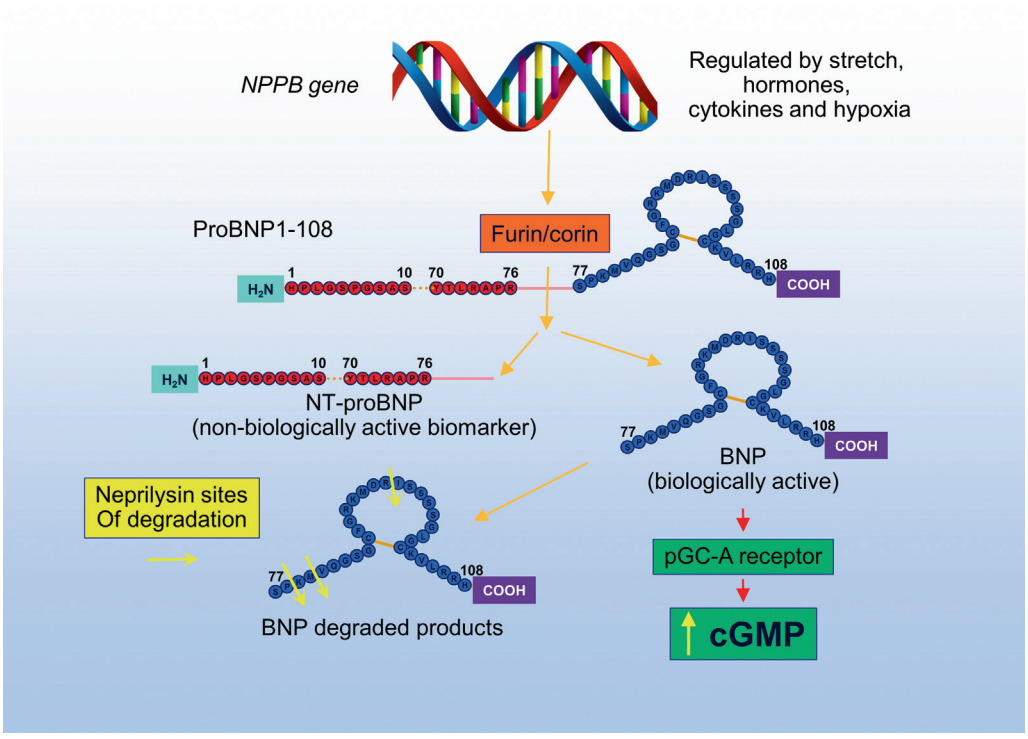
FIGURE 1 Synthesis of ProBNP From the BNP (*NPPB*) Gene



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 of NT-proBNP in a large (>8,000 subjects), international, and randomized trial with positive outcomes for HF-related mortality and morbidity. Indeed, the clinically significant reduction in hospitalization and death with ARNi therapy compared with enalapril is speculated to be in part secondary to the 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 pg/ml and follow-up NT-proBNP levels at 1 and 8 months. Impressively, as early as at 1 month, the NT-proBNP decreased below 1,000 pg/ml in 24% of participants, and the reduction from above to below 1,000 pg/ml was associated with improved outcomes when compared with participants whose levels

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 previous studies that demonstrated the greater prognostic utility of NT-proBNP over BNP, it may be that approval of ARNi therapy will further push the transition away from BNP to NT-proBNP.

Several intriguing questions emerge from this study. First, why was there a greater reduction in NT-proBNP with the ARNi therapy compared with enalapril? One potential explanation is simply greater hemodynamic unloading with less myocardial stretch 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 multi-biomarker 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 on an important and well-executed study on the prognostic utility of changes in NT-proBNP in response to ARNi therapy.

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