



## Editorial

# Neurohormones in heart failure: predicting outcomes, optimizing care

Michael M. Givertz, Eugene Braunwald\*

Cardiovascular Division, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, USA

Received 11 December 2003; accepted 12 December 2003

This editorial refers to "The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT" by R. Latini et al. on page 292<sup>†</sup>

As both the prevalence of heart failure (HF) and the number of therapeutic modalities for this condition grow, the search for improved biomarkers to predict prognosis and guide therapy continues. In this issue of the *European Heart Journal*, Latini et al.<sup>1</sup> report on the relative prognostic value of plasma neurohormones in HF by analysing the relationship between six biomarkers and outcomes in 4300 patients in the Valsartan in Heart Failure Trial (Val-HeFT). Although on univariate analysis all six neurohormones (Endothelin-1, Big Endothelin-1, aldosterone, plasma renin activity (PRA), B-type natriuretic peptide (BNP) and plasma norepinephrine (PNE)) were significant predictors of mortality, in a multivariate analysis only the latter two remained strong predictors. These new data raise the interesting question of how these two neurohormones can now be used to optimize patient care.

## Neurohormonal activation and outcomes in heart failure

Numerous lines of evidence support the idea that neurohormonal activation contributes to ventricular remodelling and disease progression in HF. Elevations of PNE in HF, with a correlation between the level of PNE and the clinical severity of HF, were described in 1962.<sup>2</sup> In 1984, Cohn et al.<sup>3</sup> reported that PNE is *independently* associated with mortality in patients with advanced HF. Subsequent studies demonstrated a strong inverse relationship between circulating PNE and survival in patients with asymptomatic LV dysfunction, and with LV dysfunction post-MI. While most studies measured neurohormones at baseline and assessed their relationship to subsequent

clinical events, the Val-HeFT investigators demonstrated that the change in PNE over 4 to 12 months was also independently associated with morbidity and mortality.<sup>4</sup>

## Should reducing PNE be a goal of therapy?

The adverse effects of chronic adrenergic stimulation in HF have been well characterized and include ventricular and vascular remodelling, as well as proarrhythmia. Furthermore, the success of beta-blockers in improving outcomes emphasizes the importance of therapy that targets the sympathetic nervous system, and raises the question of whether reducing PNE should be a primary goal of therapy. However, available evidence does *not* support such a goal. ACE inhibitors and beta-blockers exert potent beneficial effects on survival, but have variable effects on PNE. For example, in the CONSENSUS trial, enalapril reduced mortality by 27% in severe HF, but had no effect on PNE. Similarly, both carvedilol and cardiac resynchronization therapy cause reverse ventricular remodelling in dilated cardiomyopathy *without* decreasing PNE. Conversely, other therapies that reduce PNE have neutral or adverse effects in HF. For example, moxonidine, a potent central sympatholytic agent, profoundly reduces PNE but appears to *increase* mortality and the risk of MI. Similarly, a study of ibopamine in severe HF was stopped early due to excess mortality despite a reduction in PNE.

## Limitations of measuring PNE

While Latini et al.<sup>1</sup> have shown in this large contemporary well-treated population of patients with HF that PNE remains a powerful independent predictor of morbidity and mortality, measurement requires high-performance liquid chromatography, which is time consuming and is not readily available for routine clinical care, certainly not at points of care. Thus, despite the strong pathophysiologic rationale for measuring catecholamines in HF, practical considerations suggest that PNE is sub-optimal as a *routine* biomarker for clinical purposes.

\* Correspondence to: Eugene Braunwald, MD, TIMI Study Group, 350 Longwood Avenue First Floor, Boston MA 02115, USA. Tel: 617-732-8989; Fax: 617-975-0955

E-mail address: ebraunwald@partners.org (E. Braunwald).

<sup>†</sup> doi:10.1016/j.ehj.2003.10.030

## Natriuretic peptides: initial observations and prognostic value

Since the initial observation of small granules in guinea pig atria a half century ago, intense investigation has sought to understand better the structure and function of natriuretic peptides. Myocardial expression of ANP and BNP is increased in HF, and elevated plasma levels correlate with disease severity. In contrast to the other neurohormones elevated in HF, natriuretic peptides appear to serve an adaptive counter regulatory role. For example, in addition to vasodilator and diuretic effects, BNP exerts positive lusitropic and antifibrotic effects in failing myocardium. The rationale for using ANP and BNP as surrogates for clinical status is based on numerous correlations between natriuretic peptides and haemodynamics, symptoms and functional capacity in a broad range of HF patients.<sup>5</sup>

Initial studies found that patients with supra-median levels of ANP had greater neurohormonal activation, more arrhythmias, worse haemodynamics, and impaired survival. BNP levels also predict the risk of sudden cardiac death and the need for cardiac transplantation.<sup>5</sup> Latini et al.<sup>1</sup> report that BNP is superior to other neurohormones (including PNE and PRA) as a prognostic marker in HF. BNP is a powerful predictor of all-cause mortality in HF, independent of other known prognostic factors.<sup>4</sup> Latini et al.<sup>1</sup> have extended this finding to patients on ACE inhibitors and beta-blockers.

Other therapies that improve survival in HF, including carvedilol and spironolactone, have also been shown to reduce BNP. However, not all favourable interventions in HF lowered BNP. Thus, cardiac resynchronization therapy does not appear to affect BNP, while implantable cardioverter defibrillators may actually be associated with an increase in this neurohormone.

### Can BNP predict the response to therapy?

In addition to predicting outcomes, BNP may also predict the response to therapy. In the report by Latini et al.,<sup>1</sup> there was a trend towards a beneficial effect of valsartan in patients with high BNP, while PNE had no predictive power in this regard. In the Australian-New Zealand Heart Failure study, patients with high BNP but low PNE showed the greatest response to carvedilol, including a >90% reduction in HF hospitalizations.<sup>6</sup> In patients with end-stage HF, a rapid fall in BNP following implantation of a left ventricular assist device predicts recovery of LV function.

Changes in BNP levels during treatment of decompensated HF may also have prognostic value. A direct relationship between the change in BNP and adverse outcomes was noted in Val-HeFT.<sup>4</sup> Cheng et al.<sup>7</sup> reported that increase in BNP was associated with mortality or readmission with heart failure, whereas BNP declined in those without an adverse outcome. In another study, BNP levels measured prior to hospital discharge were superior both to clinical findings and other biomarkers in identifying patients at increased risk for cardiovascular death. Sustained elevations in BNP may be an independent

predictor of mortality. In Val-HeFT, treatment with the angiotensin receptor blocker valsartan caused a sustained reduction in BNP, although this effect was attenuated in patients on both an ACE inhibitor and beta-blocker. Encouraging pilot studies have suggested a role for BNP-guided therapy in the outpatient setting. Taken together, these data argue in favour of tailoring therapy to lower BNP levels in acute and chronic HF.

### Practical considerations in measuring BNP

In contrast to PNE, BNP is sensitive and relatively specific for HF, has a low coefficient of variation, and can be measured rapidly and reliably by a point-of-care immunofluorometric assay or a newer monoclonal assay. However, clinicians must consider important biological variability when managing individual patients. BNP levels increase with age, hypertension, renal insufficiency and female gender, and decrease with obesity and preserved ejection fraction. Other co-morbidities that may increase BNP include myocardial ischaemia, atrial fibrillation, and sleep apnea.

### Conclusions

The important contribution of Latini et al.<sup>1</sup> is the comparison between six neurohormones in a single, large, well-characterized population. While most previous efforts have focused on neurohormones that contribute to ventricular remodelling and disease progression, BNP has now emerged as the strongest predictor of morbidity and mortality despite its counter regulatory role. In addition, BNP appears to track changes in clinical status and the accumulating observations on this neurohormone now suggest strongly that BNP levels may be used to optimize care of the patient with HF.<sup>8</sup>

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