EDITORIAL COMMENT

Serial Measurements of Plasma B-Type Natriuretic Peptides

What Do They Tell Us?*

A. Mark Richards, MD, PhD, DSc, FRCP, FRACP
Christchurch, Canterbury, New Zealand

Circulating B-type natriuretic peptides (BNP and N-terminal part of the pro-B-type natriuretic peptide [NT-proBNP]) increase in proportion to cardiac dysfunction, and plasma concentrations are powerful independent predictors of outcome across the spectrum of cardiovascular disease. Most reports underpinning the prognostic utility of plasma B-type peptides rely on analyses derived from single measurements per study participant. Such isolated measurements improve risk stratification at any time during progression of chronic heart failure (CHF). Less is known about additional information to be gained from serial peptide measurements. Changes in either BNP or NT-proBNP over brief periods are related to subsequent outcomes in both acute coronary syndromes and acute decompensated heart failure (HF) (1,2). Changes in NT-proBNP over months predict outcome in advanced HF (3). The relationship between changes in peptide levels over longer intervals with outcomes in a large group with stable CHF has been explored for BNP (4) but not NT-proBNP.

See page 997

In this issue of the Journal, Masson et al. (5) examined the prognostic value of changes in NT-proBNP between baseline and 4 months in 1,742 patients randomized to the placebo arm of the Val-HeFT (Valsartan Heart Failure Trial) study. Changes in NT-proBNP expressed as absolute, percent, or categorical change were related to subsequent mortality. Absolute change in plasma NT-proBNP in quartiles (Q) showed a U-shaped relationship to subsequent mortality (15.1%, 8.3%, 11.5%, and 26.4% in Q1 to Q4, respectively), whereas mortality increased incrementally across quartiles of percent change in NT-proBNP (from 9.2% in Q1 to 21.5% in Q4). In a third approach, outcomes were assessed according to categorical changes of NT-proBNP. In patients with results below the nominated threshold (1,078 pg/ml) at baseline and 4 months (52% of patients), with values above decreasing to below (7.2%), below increasing to above (6.5%), and with both values above the threshold (34%), mortality rates were 8.9%, 7.2%, 21.1%, and 25.7%, respectively. Multivariable analysis including adjustment for age, body mass index, renal function, etiology, New York Heart Association functional class, left ventricular function, and baseline NT-proBNP indicated categories were independently associated with mortality.

This report is the most recent in a series arising from the Val-HeFT neurohormonal substudy. The Val-HeFT study showed BNP to be prognostically superior to several other recognised neurohormonal markers of risk in HF, including norepinephrine, renin activity, aldosterone, and endothelin (6). In a head-to-head comparison of BNP and NT-proBNP including 3,916 Val-HeFT study participants (7), baseline BNP and NT-proBNP were powerfully and similarly related to both mortality and risk of admission with decompensated HF independent of, and more strongly than, any of a range of pertinent predictive demographic, clinical, and echocardiographic variables.

From results in 4,305 patients, Anand et al. (8) reported an association between mortality and both baseline BNP (9.7%, 14.3%, 20.7%, and 32.4% in Q1 to Q4, respectively) and percent change (13.6%, 15.5%, 15.1%, and 19.1%, in Q1 to Q4, respectively) in BNP. Subsequently, Masson et al. (4) assessed categorical change about the baseline median level of BNP (97 pg/ml). Results from 3,740 patients indicated categorical divisions of low→low, high→low, low→high, and high→high in the 4-month interval were associated with 2-year mortalities of 7.9%, 12.8%, 22.7%, and 25.4%, respectively; these are highly comparable with rates (8.9%, 7.2%, 21.1%, and 25.7%) reported currently for categorical shifts in NT-proBNP levels (5).

Taken together, the Val-HeFT study experience indicates that changes in either BNP or NT-proBNP over months are predictive of outcomes in chronic HF. This offers the prospect of several applications, including monitoring of cardiac compensation and guidance of HF therapy, selection of higher-risk subjects for recruitment to therapeutic trials (improving power and reducing requisite sample size), and potentially providing a reliable surrogate index of efficacy of new treatments.

However, it remains debatable whether changes in peptide levels offer significant practical advantages over single measurements. Within the current report, the ascending risk of subsequent mortality according to the baseline
quartile of NT-proBNP levels (7.8% increasing to 25.3% from Q1 to Q4) suggests similar discrimination to that derived from categorical shifts (7.2% increasing to 25.7% risk). Absolute NT-proBNP values at 4 months outperformed baseline values, as well as both absolute and percentage change in prediction of all-cause mortality at 24 months by receiver-operator analysis. The investigators do not present a multivariable model assessing the prognostic power of categorical shifts independent of 4-month NT-proBNP values, nor do they report mortality by quartile of 4-month NT-proBNP levels. It remains possible that the best single indicator of subsequent outcomes (and the most practical tool for the applications outlined above) is simply the single most recently available measurement of BNP or NT-proBNP.

The categorical threshold value of 1,078 pg/ml was derived from receiver-operator analysis of the optimal NT-proBNP value for discriminating risk of later mortality, a value that can only be established once mortality over follow-up has occurred. Clearly this is not a value that can be discerned prospectively. The earlier Val-HeFT study report assessing categorical shifts of BNP used the median baseline level of BNP (97 pg/ml), and such values would of course be available from the outset during follow-up of any given cohort of chronic HF patients. Nevertheless, it is unlikely that categorical shifts around threshold values of approximately 100 and 1,000 pg/ml for BNP and NT-proBNP, respectively, can be practically or uniformly applied to individuals or even to other cohorts with HF. Intuitively, an individual patient with values increasing from just below to barely above a threshold seems at less risk than another with NT-proBNP increasing from a similar initial value to a markedly higher final level. Yet both patients show the same categorical shift and may be lumped together with same apparent mortality risk. Consideration of percent changes would seem less prone to this weakness.

The BNP and NT-proBNP values of 100 and 1,000 pg/ml, respectively, are higher than median levels observed changes would seem less prone to this weakness.

Finally, the prognostic utility of changes in B-type peptide levels will be enhanced by proper integration with other known markers of prognosis. Combining cardiac imaging with cardiac peptide measurements to better define prognosis seems to hold particular promise. Notably, the Val-HeFT study incorporated serial echocardiography, providing the opportunity to undertake such an analysis.

Reprint requests and correspondence: Dr. A. Mark Richards, Christchurch School of Medicine and Health Sciences, Department of Medicine, Riccarton Avenue, P.O. Box 4345, Christchurch, Canterbury 8140, New Zealand. E-mail: mark.richards@cdhb.govt.nz.

REFERENCES


Key Words: heart failure • NT-proBNP • BNP • risk stratification • prognosis in heart failure • cardiac natriuretic peptides.